BIH Mission and Implementation

Working Draft, April 2020

Berlin Institute of Health
Charité & MDC

Turning Research into Health

bihealth.org

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Mission

The mission of the BIH (Berlin Institute of Health) is to facilitate the translation of findings from biomedical research into new approaches to diagnostics, personalized prediction, prevention and therapy and, conversely, to utilize clinical findings to help researchers develop novel approaches. The aim is to deliver relevant medical benefits for patients.

Translation

Medical need

Health systems in Germany and around the world are facing major challenges. With aging populations leading to more patients, and at a time that there are fewer nurses and care workers, medical research will be pivotal in providing us with fresh insights into new models of care and treatment. In addition, while digitization promises to deliver a network of information from a wide variety of sources that support research, the medical world must become more successful in bringing solution-oriented observations and the questions raised by everyday clinical practice into translational research. The reverse process, the transfer of observations from the laboratory back to everyday clinical practice, also needs to be improved and accelerated.

With no long-term treatment options currently existing for many diseases, the hope of future successes in treatments for a range of conditions hinges on the rapid technological progress being made in basic research and information technology. Such a scenario makes it vital to combine innovative technologies and research activities with clinical expertise that is driven by medical need, thus establishing new medical, technical and digital solutions within a reasonable timeframe. This is one of the core tasks of the BIH. Being based in Berlin, the BIH sits in the ideal location for fulfilling this mission by offering easy access to biomedical research from a large number of university and non-university working groups. The Charité, as Europe's largest university clinic, is not only able to deliver clinical excellence in a wide range of areas, but also has a broad spectrum of patients - all the components needed for the successful development of new forms of therapy within this biomedical 'ecosystem.'

Challenges

Currently, the translation of innovative approaches into clinical practice requires much in the way of time and resources, and unfortunately is often not as successful as it could be. Available data shows that the number of approved drugs per billion USD (adjusted for inflation) in research investments has on average halved every nine years since 1950.[1]

A major reason for this decline is the ***complexity of the steps required along the translational value chain***, from innovative idea to real-world clinical application. In addition, a multitude of infrastructures and technologies, as well as professional groups with different skill sets, are required to contribute to the process and work towards a common goal.

[1] *Derek Lowe, Science Translational Medicine, 2012*

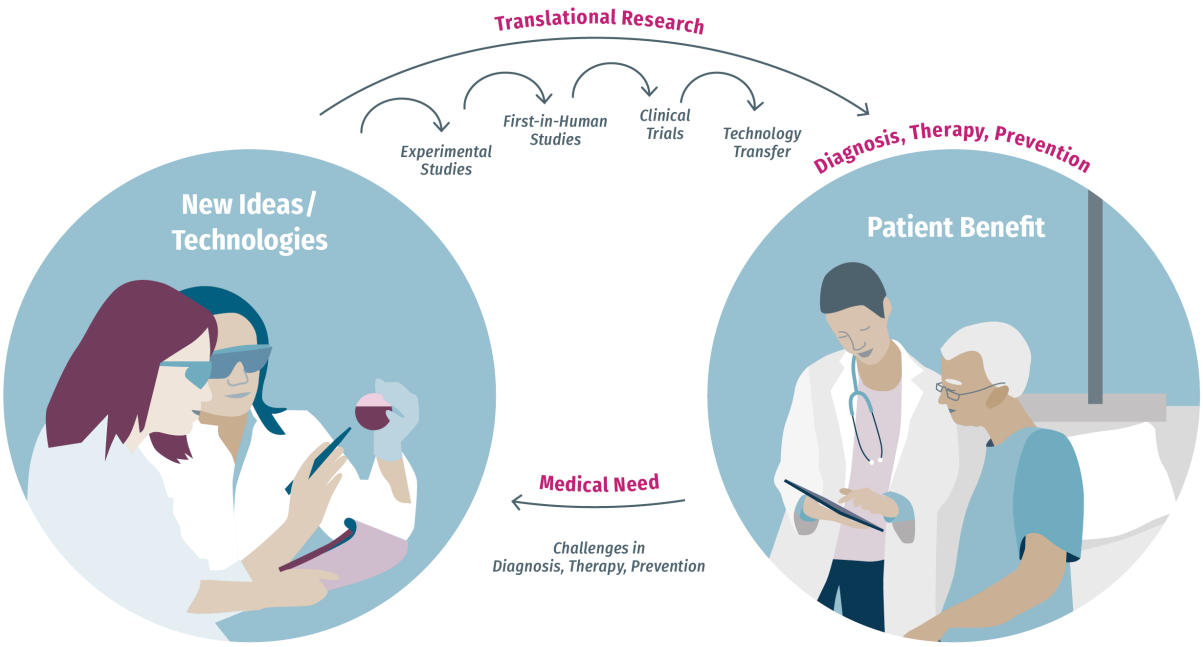

Figure 1: The Translational Value Chain

However, another challenge lies in the combinations of people involved in these various stages, who often have different priorities, speak different languages and work in different communities. For scientists working in basic research, an understanding of new molecular mechanisms - and subsequently publishing results in well-known journals - is crucial. Sitting opposite this, for translational research to be successful in delivering achievement from preclinical and clinical studies, there is a need for all clinical partners and researchers involved in the process to share common goals and cooperate closely from the very beginning. Greater cohesion is of the utmost importance here - underlining the importance of those involved in both basic and translational research to possess the capabilities and skill sets needed to master the complex requirements for the preparation and approval of clinical trials. These steps, however, require considerable time and resources and may not always seem worthwhile in the basic research environment. Such hurdles and difficulties exist at many interfaces of translational value creation and can lead to the development of separated silos, endangering the effectiveness of the translational process.

Yet translation cannot, and should not, be divided into 'basic scientific knowledge' and 'implementation in clinical practice'. On the contrary, translation-oriented teams and facilities must both be anchored in the clinic, and in the laboratory. Professionals working in daily clinical practice observe medical need through contact with patients or through the help of innovative big data processes, whilst pathophysiological research approaches and therapy concepts can be developed through interaction with scientists in basic research and reviewing them based on medical need. The necessary 'mindset' for translation can only arise within this context.[2]

[2] *Key elements for nourishing the translational research environment.* Sci Transl Med. 2015; Volk, Stevens, Mooney, Grainger, and Duda;
DFG Stellungnahme zur Translation
https://www.dfg.de/download/pdf/dfg_im_profil/reden_stellungnahmen/2019/190919_stellungnahme_empfehlung_ag_translation.pdf

Another challenge for medical translation is the pathophysiological limits of ***traditional, organ-oriented, concepts*** in medicine and research. These promote a deep understanding of individual structures, but do not take sufficient account of the fact that the different functions and structures within an organism are closely linked; physiological and pathological mechanisms overlap, and genetics and the environment affect all organs and systems simultaneously. Most chronic diseases occur when processes that affect the whole body fail. These include the body's immune system and inflammatory processes, blood circulation or the regeneration of tissue lost through trauma or degeneration.

At the same time, fundamentally new opportunities are opening up for translational medicine through the digital revolution including new technologies such as: machine learning/artificial intelligence, biomimetic materials, 3D printing, human-on-a-chip, pluripotent stem cells, organoids, genome editing, the dramatically increasing level of detail and speed of molecular analysis (omics: genomics, proteomics, metabolomics), as well as new approaches in diagnostics and therapy development at the cellular level. As an example, Novel Therapies (Advanced Therapy Medicinal Products - ATMP) - a new class of personalized therapeutics at the cellular basis (Living Medicines) - offer new options for more effective translation in the area of academic research.

BIH Approach

The BIH is not a typical research institute. Its innovative approach is to utilize a novel concept of clinically-anchored cross-organ systems medicine in a comprehensive translational ecosystem to significantly increase the speed and effectiveness of medical translation. One of the main reasons for the success it enjoys in translational research is the clinical and scientific environment at the Charité and across Berlin, enabling a high degree of interaction due to the proximity of different partners. The MDC (Max Delbrück Center for Molecular Medicine) is central to the development of technologies and new mechanistic approaches.

The BIH Translational Ecosystem

By establishing comprehensive and coordinated structures in one location, the BIH is able to successfully and efficiently implement its mission of medical translation. Such an approach enables the various professional groups involved to use their expertise to establish new preventive strategies, develop new diagnostics and effective therapies, and to discover how these options can be effective for patients. Together with Charité and MDC, the BIH has established a comprehensive translational value creation system.

In order to transfer new concepts into clinical practice faster and more effectively, it is important that the parties involved are networked in a translation-oriented environment - the ***translational ecosystem***. The BIH ecosystem bundles a variety of competencies and infrastructures in the vicinity of the Charité clinical facilities, confirming the findings that:

• translational processes are usually not linear and targeted, as suggested by the concept of the translational value chain; and

• a variety of skills, infrastructures and support mechanisms are essential for effective translation

This ecosystem is unique to the BIH. It encompasses the necessary critical mass of all professions and skills required, and provides the necessary structures and services for translation. As such, this environment allows continuous optimization of ideas and solutions in one iterative ***'bench to bedside'*** and ***'bedside to bench'*** process. Crucial for the achievement of the BIH mission is the continuous development of the ecosystem as a learning system. The experience gathered from all projects and processes, and new ideas and concepts from the faculty and benchmarks from other institutions, contribute to this.

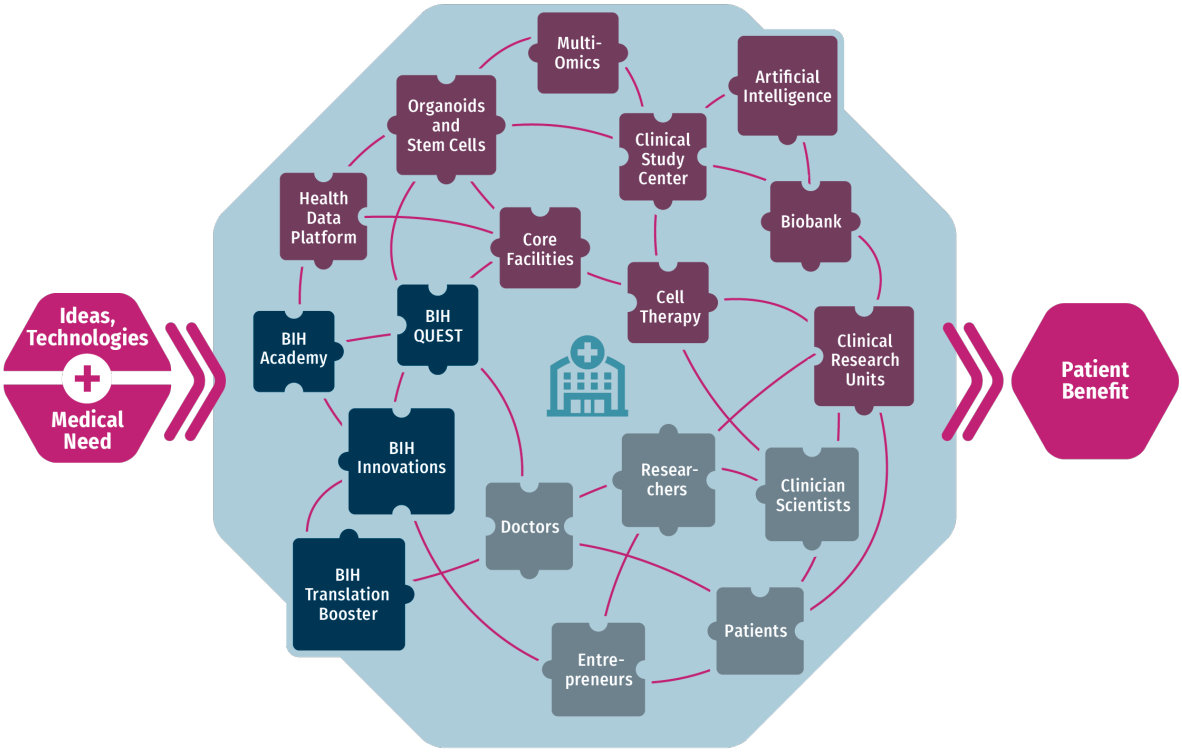

Figure 2: The translational Ecosystem of BIH

Cross-Organ Systems Medicine

The BIH focuses on cross-cutting issues: for example, digital medicine, and cell-based therapies as innovative drivers and enablers; and not organ-specific approaches such as cardiology and cancer research. The BIH, thus, works across systems medicine, examining processes that arise from the interaction of various organs and systems in the body.

The systems medicine translation approach at the BIH is therefore a necessary addition to the disciplinarily oriented approach of the German Centers for Health Research, which uses a decentralized network of expertise at several locations, with each focusing on widespread diseases.

Principles

The way the BIH works can be described by the following principles:

Full Circle Together with the Charité and other stakeholders, the BIH is building a comprehensive translational value creation system. Ideas from the laboratory are transferred to the bedside and checked there **('bench to clinical reality')**. The observations in the clinic are carried back to the laboratory **('clinical challenges to bench')** and stimulate the development of new ideas and technologies.

One-Campus Interdisciplinary translation is made possible at the BIH as all participants are able to continuously exchange ideas. The essential prerequisites **of innovation, the clinic and implementation**, are available on site and can be utilized without institutional barriers. This particularly applies to clinically-obtained data, which is made available to research, whilst ensuring the highest levels of data protection.

Interdisciplinarity **The BIH's 'translational scientific community'** includes medical professionals, basic research scientists, innovators (i.e. scientists who give the impetus for clinical application without commercial interest themselves), engineers, digital experts and data scientists, business developers, entrepreneurs, market analysts, health system experts, as well as the users, and particularly, patients.

Partnering To ensure excellence at all stages of the translation process and to be able to fund application-related phases, the BIH adds to its expertise and resources through cooperation with prominent partners from science and industry.

Decide-Early The BIH continuously analyzes projects at all levels of the translational value chain in order to either specifically promote them, or where necessary, to terminate them early. This increases overall effectiveness and reduces the risk of failure in the later, cost-intensive, stages.

Value Research at the BIH must be reliable, robust and transparent. It must be effective for science and of benefit to the wider society, and it must be proportionate to the risks and burdens taken.

Responsibility The BIH takes its responsibility towards patients and citizens extremely seriously. This is reflected in their participation, and appropriate representation, in the BIH processes and all within a gender and diversity-sensitive organizational culture with a continuous focus on relevant medical needs.

Implementation at the BIH

To fulfill its mission, the BIH's translational ecosystem is based on three components: ***innovation enablers, translation hubs,*** and ***focus areas***. These three components provide different support mechanisms for the translational process and the implementation of specific projects with a high level of innovation and translational potential. While the development of the translational environment is a continuous task that affects the entire faculty, highly-relevant questions from the various focus areas can be addressed by experts in the respective translational fields and adapted dynamically to scientific and clinical development.

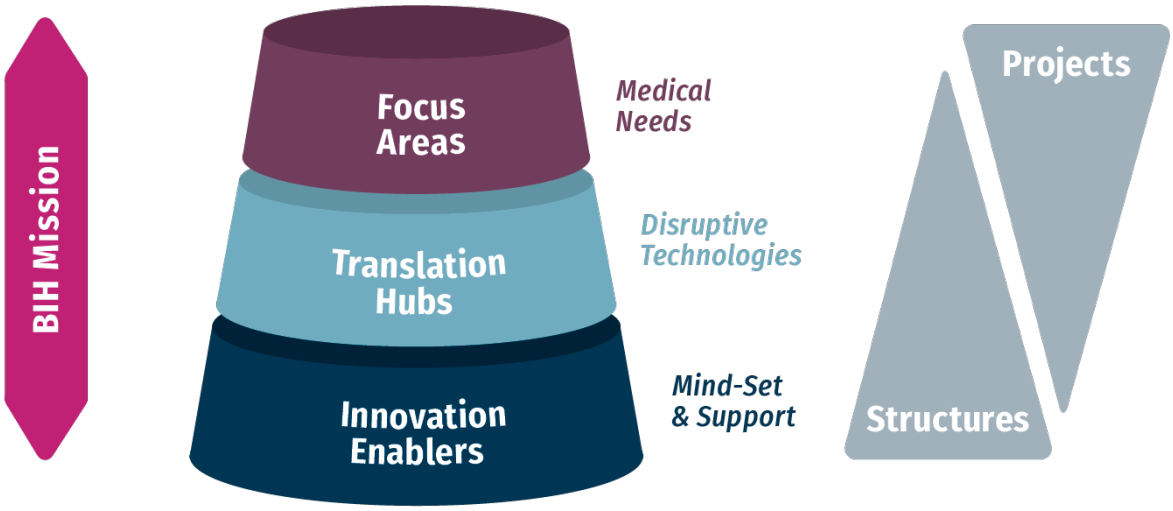

Figure 3: The components of BIH

Innovation Enablers

The basis of the ecosystem is the **translation-oriented mindset** of all stakeholders involved in the process and the constant support of the faculty in all phases of translation. Developing this is the task of the BIH's four **innovation enablers**: the *BIH Academy* (BIA) continuously promotes doctors and scientists with translational skills and interests, designs specific further-education programs, and identifies group-specific career paths; the BIH-QUEST Center has developed and implemented new approaches to ensure the quality and sustainability of research through all phases of the value chain; the BIH-Translation-Booster develops mechanisms and incentives to overcome the hurdles along the chain; and *BIH-Innovations* promotes the early, and targeted, transfer of innovative ideas into products and clinical solutions at all levels of translation.

BIH-Academy	*Competencies*	Task Approach Incentivization	Develop commitment and competence in translation Support career development Training program
QUEST	*Quality*	Task Approach Incentivization	Ensure optimal use of resources Establish quality and sustainability Value-Incentives
BIH-Accelerator	*Efficacy*	Task Approach Incentivization	Increase the speed and effectiveness of translation Overcome hurdles Translation-Incentives
BIH-Innovations	*Transfer*	Task Approach Incentivization	Use the potential of innovations and products Establish the mechanisms for translation Innovation-Incentives

Figure 4: The Innovation Enablers of BIH

These four functions are essential in all areas of medical translation. However, as they do not directly address organ-oriented medical questions, they are not usually the focus of translational initiatives. To address this, and add a further dimension to the effectiveness of translation, the BIH has set up the innovation enablers to optimize conditions for the development and maintenance of the translational 'mindset' and 'support' over the long term. The incentive mechanisms of value, translation and innovation services complement the classic performance-oriented allocation of funds, which rewards publications and third-party fundraising.

It is very important to avoid an oversimplified interpretation of the translational value chain. The focus of translational efforts in the academic environment is usually a question of whether new concepts and ideas can be implemented scientifically and clinically (point 1 in Fig. 5). However, such a narrow view can often lead to project failure in later phases and to the inefficient use of resources. Reasons for this can include the inadequate validity and robustness of data from the earlier stages, or a lack of foresight when examining legal and economic aspects.

Such deficits are avoided in the BIH's translational ecosystem through BIH-Innovations and the BIH-Translation-Booster examining ideas with high translational potential at the early stage with scientific and transfer aspects in mind and continuously supporting the parties involved in the process as early as possible. In this way, feasibility in terms of technology, legal, financial and organizational aspects (points 2 and 3) can be clarified early on in order to launch larger numbers of highly innovative and riskier projects into the translational ecosystem based on this "decide-early" principle. The services offered by the innovation enablers are generally available to the entire scientific community, thus helping to continuously create the best conditions for concrete translational approaches.

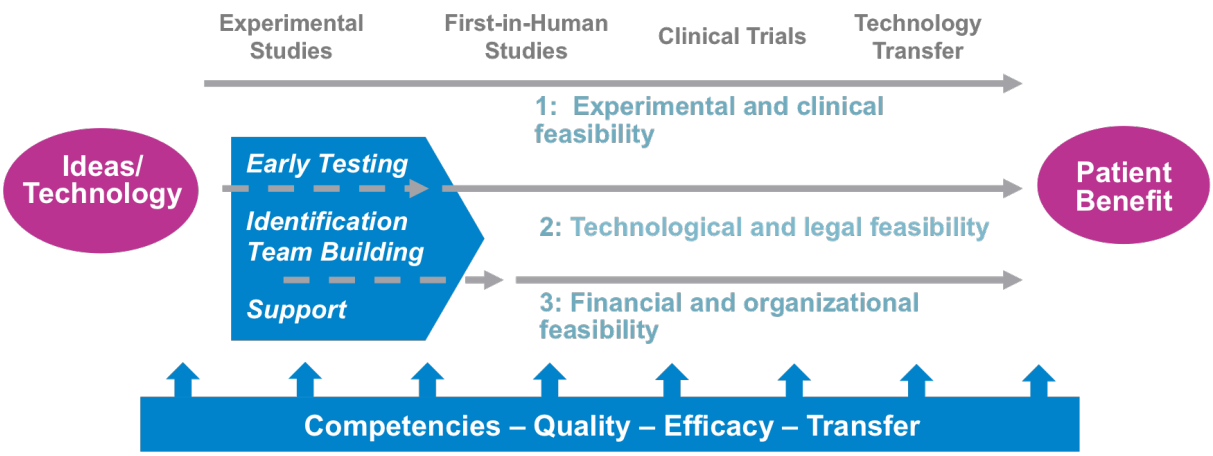

Figure 5: The Role of the Innovation Enablers in the translational Ecosystem of BIH

Translations Hubs

Each translational institution must select which research and development priorities it wants to focus its activities and resources on. This takes place at the BIH within the translation hubs and focus areas. In accordance with the strategic decision for a cross-organ approach, the BIH has selected topics that can make fundamental systems medicine contributions to translation.

The ***translation hubs*** represent topics and ***technologies that will revolutionize medicine across various disciplines in the coming years:***

- Digital Medicine
- Multi-Omics
- Organoids and Cell Engineering
- Clinical Translation

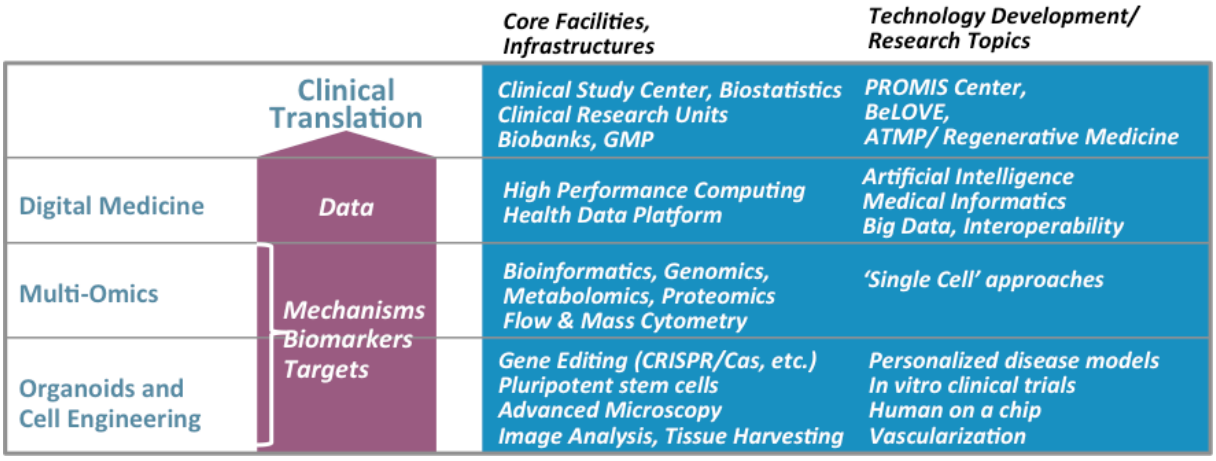

Figure 6: The Translation Hubs of BIH

In these areas in particular, highly relevant contributions can be made to the BIH's translational mission and to improving clinical options for patients. The translation hub Digital Medicine enables the extensive use of data-based approaches; Multi-Omics ensures phenotyping at the highest level; and Organoids and Cell Engineering make the targeted modulation of cells and 3D organ cultures usable for innovative, precision-based medical approaches. The translation hubs support effective translational research through the Clinical Translation hub by:

- ***Networking*** experts and establishing a research community
- ***Developing*** innovative technologies and methods
- ***Providing*** excellence in scientific services (core facilities)

Focus Areas

The ***focus areas*** bring concrete translational research and development projects into the translational ecosystem. These focus areas are characterized by:

- taking a systems medicine approach
- having a high potential for groundbreaking success in translation
- successful and decisive implementation in the translational ecosystem

Vascular Biomedicine	(Micro-)vascular dysfunction is a cross-organ pathogenic mechanism contributing to disease in many organ systems
Single Cell Approaches	Single Cell technologies are driving a paradigm shift in understanding genome function in the development and treatment of disease
Regenerative Therapies	Advanced therapies and living drugs are opening up fundamentally new possibilities for regeneration
Excellence Fund Projects	Projects with high potential for translation

Figure 7: The Focus Areas of BIH

Three focus areas have been established at the BIH, each using different elements of the BIH's translational value chain ***('regenerative therapies', 'vascular biomedicine', and 'single cell approaches for personalized medicine').*** The relevance of these, as well as the excellence achieved by the parties involved, is clear from the extraordinary fact that from across all scientific fields, two areas ('regenerative therapies' and 'single cell approaches for personalized medicine') have made it to the final selection round of the last six 'European FET Flagships'. Focus areas are fundamentally dynamic and are continuously adapting to scientific, technological and translational developments.

The integration of both the available expertise necessary for research projects with that not available on site, as well as the piloting of concepts and technologies particularly relevant for translation, is carried out via the dynamic ***'Excellence Fund'***. High-risk projects with high potential are given the opportunity to show evidence of medical added value through temporary funding and to connect with external funding agencies.

Success Criteria and Exploiting the Potential of the BIH

As the BIH's translational approach differs significantly from other basic research institutes, it is essential to develop new criteria for evaluating the success of the BIH that go well beyond the usual indicators, such as impact factors or third-party funding. The success of translational research cannot be measured in terms of the number of individual publications and, as a rule, cannot be assigned purely to individuals. Both ***specific criteria for translational projects*** (see below) and new evaluation principles for researchers working in translational research must therefore be defined.

Specific indicators must focus on the BIH mission, i.e. reflect the relevant medical benefits for patients. Direct parameters for this goal include:

- Introduction of new preventive, diagnostic and therapeutic procedures into the clinic
- Products and launches
- Changes to guidelines, treatment and therapy guidelines
- Returns from sales and licensing
- Social added value (virtual proceeds)
- PROMS (Patient Reported Outcome Measures)

These direct indicators only emerge at the end of the successful translation and, therefore, with a considerable delay in the important preparatory steps. However, these contributions are indispensable and can also be measured at short notice. They also need to be assessed and incentivized:

- Proof of principle studies
- Manufacturing permits, etc.
- First in human - studies and clinical studies based on own concepts (IIT)
- Ratio: from number of patents or patent applications to patents being used
- Licensing, spin-offs and corresponding cooperation

Also relevant for the BIH strategy are additional parameters that assess quality and sustainability at all levels of translation, such as:

- Open Access publications
- Open Data/Open Science
- Publication of negative results
- Confirmatory Studies

The BIH-QUEST-Center has launched important initiatives for BIH and Charité in recent years in this area, which have led to a significant increase in open data publications and have been acknowledged both nationally and internationally.

In order to further develop structures and mechanisms for translation, the BIH became the first continental European partner to cooperate with the Wellcome Trust in 2019. Within this context, parameters for measuring success and mechanisms to incentivize the different steps of translation - and the different areas and individuals in the translational ecosystem -are being developed and comparisons made with other international medical research centers, such as the National Institutes of Health (NIH). A system is being devised in which evaluation will make it possible to compare the different success criteria quantitatively.

Structurally, the BIH is a new type of scientific institution and, when integrated into the Charité, becomes a prototype for direct federal funding of higher education institutions. The involvement in the Charité enables the BIH to strive for new standards on a structural level. That ranges from education – such as the promotion of young researchers into new translational career paths - to quality assurance and structural support in the processes of a research hospital in project selection, recruitment, and entrepreneurial support.