Frontiers in Translational Medicine – Scientific and Structural Challenges

Axel R Pries
What is Translation?

"Translation is the Transfer of Basic Scientific Research Results into new Preventive, Diagnostic or Therapeutic Methods for the Application to Humans."

(DFG, Recommendations for the Promotion of Translational Research in University Medicine, 2019)

From Wikipedia, the free encyclopedia

Translational medicine (often referred to as translational science, of which it is a form) is defined by the European Society for Translational Medicine (EUSTM) as "an interdisciplinary branch of the biomedical field supported by three main pillars: benchside, bedside, and community".[1] The goal of TM is to combine disciplines, resources, expertise, and techniques within these pillars to promote enhancements in prevention, diagnosis, and therapies. Accordingly, translational medicine is a highly interdisciplinary field, the primary goal of which is to coalesce assets of various natures within the individual pillars in order to improve the global healthcare system significantly.[1]
Medical Need: Why Do We Need Translation?

Desired Scenario

Health

Years of Life

Chronic Disease

Health

Years of Life

Aim of Translation:
Increase Integral Quality of Life
The Translational Value Chain

- Ideas
- Technology

Exploration

in vitro
in silico

Basic Studies
First in Man
Safety
Proof of Concept
Clinical Trials
Technology Transfer
Product
Health Services
Research
Population Health

Medical needs

Start Ups
Academia
Clinics
Industry
Health Providers

Number of Concepts

Cost
Status of Translation
Too slow, too expensive

Erooms Law:
The cost of developing a new drug doubles approximately every nine years.

Diagnosing the decline in pharmaceutical R&D efficiency

Jack W. Scannell, Alex Blanckley, Helen Boldon & Brian Warrington

Nature Reviews Drug Discovery 11, 191–200 (2012) | Cite this article
Causes
“Local Cultures”

Academia
Nature/Science Paper
Impact
Visibility
Patient
Benefit

Publications and external funding determine success, research opportunities and career
Academia

Publications and external funding determine success, research opportunities and career

Nature/Science Paper  ->  Impact Visibility

Translation

Translational steps are expensive, time consuming and require many competencies

Manufacturing Authorisation  ->  First-in-Human Study

Causes

“Local Cultures”
Causes
“Happy Silos”

Academia

- Bibliometrics
- External Funding

Clinics

- Payment/Cost Ratio

Industry

- Return on Investment

Insurance

- Treatment-Cost Attractivity

Ideas Technology

Patient Benefit
Causes

Not Sufficiently Addressed:

*High Complexity of Translation*

Overarching Disease Mechanisms
An Unexpected Hurdle in Drug Development
An Unexpected Hurdle in Drug Development

Preclinical Efficacy Studies in IBs

109 Investigator Brochures (IBs) for phase I/II trials

708 Pre-Clinical Efficacy Studies (PCES)

Reference to published reports: 11%

Practices to address validity threats:
- Sample Size Calculation: 0%
- Blinded outcome assessment: 0%
- Randomization = 4%
- Sample size reported: 26%

Positive Outcome: 90%

No effect: 6%  Unclear: 4%

Lack of robustness in preclinical evidence

Daniel Strech, Translational Bioethics, QUEST
Chances

New Disruptive Technologies Meet Personalized Medicine

Precision Medicine

Optimized Therapy for Individuals

instead of

Blockbusters for Everyone

Digital Medicine

Omics

Cell Engineering
Approaches: DZG
- Best Experts from All Over Germany Focus on One Disease
BIH Approach
- Systems Medicine in a Translational Ecosystem
BIH: Core Principles

**Full Circle**

Building a comprehensive translational Value-Chain
From Bench to Clinical Reality ↔ Clinical Challenges to Bench

**Campus**

One place to bring actors, institutions, clinics and infrastructure together

**Multisector**

Community includes basic and clinical scientists, data scientists, technology expert, innovators, entrepreneurs and transfer experts

**Partnering**

Cooperation with external partners from science an industry wherever needed

**Value**

New mechanisms to ensure quality, value and robustness of processes and results
BIH: Structure - Systems Medicine in a Translational Ecosystem -

- Address Burning Questions
- Match Experts with Disruptive Technology
- Generate a Translational Mindset
- Projects Dynamic Selected
- Support Stable Required
## Translational Ecosystem

### Innovation-Enablers: Approaches and Incentives

| BIH-Academy | People | Task | Establish a faculty skilled in medical translation  
| Support personal development and careers  
| BIA - Career Support Initiatives |
| QUEST | Quality | Task | Assure optimal use of material and human resources  
| Define and assure value of research  
| Value-Incentives (VoM) |
| BIH-Accelerator | Support | Task | Increase speed and probability-of-success in translation  
| Bridge gaps in the translational process  
| Translation-Incentives (ToM) |
| BIH-Innovation | Transfer | Task | Increase effectivity of innovation transfer  
| Provide structures and support for effective transfer  
| Innovation-Incentives (IoM) |
Translational Ecosystem
Innovation-Enablers: Addressing the Value Chain

1: Scientific and Clinical Feasibility
Translational Ecosystem
Innovation-Enablers: Addressing the Value Chain

1: Scientific and Clinical Feasibility
- Basic Studies
- First in Man
- Proof of Concept
- Clinical Trials
- Technology Transfer
- Products Applications

2: Product and Legal Feasibility
- Identification
- Team Building
- Support

3: Financial and Organizational Feasibility

Quality & Value - People & Careers - Innovation & Transfer

Patient Benefit
Translational Ecosystem
Translation-Clusters: Technology and Faculty

Match Experts with Disruptive Technology
Choose

Generate a Translational Mindset

Areas With Disruptive Technological Potential
### Translational Ecosystem

**Translation-Clusters: Technology and Faculty**

<table>
<thead>
<tr>
<th>Clinical Studies</th>
<th>Clinical Study Center</th>
<th>Medical Informatics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clinical Research Units</td>
<td>Biostatistics BeLOVE</td>
</tr>
<tr>
<td><strong>Digital Medicine</strong></td>
<td>High Performance Computing</td>
<td>Artificial Intelligence</td>
</tr>
<tr>
<td></td>
<td>Health Data Platform</td>
<td>Simulation / Digital Twins</td>
</tr>
<tr>
<td><strong>Omics</strong></td>
<td>Next Generation Sequencing</td>
<td>Biobanking</td>
</tr>
<tr>
<td></td>
<td>Mass Spectrometry</td>
<td>Single Cell Approaches</td>
</tr>
<tr>
<td><strong>Cell Engineering</strong></td>
<td>Metabolomics</td>
<td>‘Human on a Chip’</td>
</tr>
<tr>
<td></td>
<td>Gene Editing</td>
<td>Organoids</td>
</tr>
<tr>
<td></td>
<td>Stem Cells</td>
<td></td>
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</tbody>
</table>
Translational Ecosystem
Focus-Areas: Address Prominant Questions

- Focus and Select
- Match Experts with Disruptive Technology
- Generate a Translational Mindset
- Address Burning Questions
Focus and Select

Criteria

- Cross-Cutting
- High Potential for Major Translational Success
- Excellent Expertise and Competencies in the Translational Ecosystem
Translational Ecosystem
Focus-Areas: Address Burning Questions

<table>
<thead>
<tr>
<th>Vascular Biomedicine</th>
<th>(Micro-)vascular dysfunction is a cross-cutting patho-mechanism contributing to many diseases in all major organ systems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single Cell Approaches</td>
<td><strong>Flagship Project ‘Life Time’</strong> Cells of a given cell type exhibit individual properties and fates – analysing and addressing that offers fundamentally new medical options</td>
</tr>
<tr>
<td>Regenerative Therapies</td>
<td><strong>Flagship Project ‘RESTORE’</strong> Advanced therapies and ‘living drugs’ will replace and supplement approaches to allow true regeneration</td>
</tr>
<tr>
<td>Excellence Fund</td>
<td>Dynamic mechanism to support initiatives with high translational potential</td>
</tr>
</tbody>
</table>
BIH: How Do We Measure the Fulfilment of Our Mission?

Mission: Research Turned Into Health

*BH is dedicated to improving the prediction of progressive diseases and developing advanced therapies for unmet medical needs in order to restore or maintain people’s quality of life.*

**Primary KPI’s**

- Introduction of new preventive, diagnostic and therapeutic options into the clinic
- Products and launches
- Changes in guidelines
- Return of investments (licensing, selling)
- PROMS (Patient Reported Outcome Measures)
BIH: How Do We Measure the Fulfilment of Our Mission?

Mission: Research Turned Into Health

BIH is dedicated to improving the prediction of progressive diseases and developing advanced therapies for unmet medical needs in order to restore or maintain people’s quality of life.

Process – KPI’s

• Proof of principle studies
• Academic first in man and clinical studies (IIT)
• Manufacturing allowance
• Ratio of filed patents to used patents
• Licensing, spin-offs, sales
• Bibliometrics
• External funding
BIH: How Do We Measure the Fulfilment of Our Mission?

Mission: Research Turned Into Health

BIH is dedicated to improving the prediction of progressive diseases and developing advanced therapies for unmet medical needs in order to restore or maintain people’s quality of life.

Quality – KPI’s

- Open Access publications
- Open Data / Open Science
- Publication of negative results
- ‘Confirmatory studies’
- Diversity
- Inclusion
- Outreach
BIH: The Partnering Concept

- Ideas Technology
- Patient Benefit

In vitro
in silico
Basic Studies
First in Man
Safety
Proof of Concept
Clinical Trials
Technology Transfer
Product
Health Services Research
Population Health

Exploration

Medical needs

Academia
Start Ups
Industry
Clinics
Health Providers

Input from external basic institutions

Cooperation with entrepreneurs

Selling, Licensing, Founding

Medical needs
Examples for Success: BIH-Regeneration

Regulatory T-Cells (Treg) for the Control of Unwanted Immune Reactions

**Medical Need**
Graft rejection in transplantation. Standard therapy (immune suppression) has many side effects

**New Concept**
Selective blockade of pathological cells

**Translational Steps**
- Preclinical Models
- Biomarkers
- GMP-Manufacturing
- Legal-Affairs

**Refined Translation**
- Next-Gen. Treg Products
- EU Grant RESHAPE (2019;13.6 Mio €)

**Patient Benefit**
Examples for Success: BIH-Innovation

Digital Labs  PRODUCT + BUILD

End-to-End Approach

Screening of Concepts

Fast-Paced Prototype Development

Iterative Solution Build

In 2.5 Years:
>50 Concepts leading to 4 Spin-Offs

Digital Health Accelerator Stage I

Digital Health Accelerator Stage II

Ideas

Patient Benefit

License Spin off Sale
Thank You
FIRST TEAMS FROM BIH DIGITAL LABS COMPLETED THEIR PRODUCTS...

**X-Cardiac: Predicting and preventing complications in intensive care units (ICU).**

**Problem:** Taxing environment of an ICU leads to complications like post operative bleeding as well as renal failure and longer and riskier stays.

**Solution/Product:** X-cardiac is a unique monitoring solution for earlier detection of complications in an ICU by machine learning (algorithms based on a cohort of approx. 50,000 patients).

**Current Status:** Minimum Viable Product (MVP) alpha version up and running. Adds a layer of clinically relevant information on routinely collected data. MVP for research use is running at 65 beds at the German Heart Center Berlin (stable operations since April 2018). Clinical validation and regulatory certification in process. Management team completed. First negotiations with investors ongoing.

**DentalXr.AI: Deep Learning for Dental Image Diagnostics.**

**Problem:** The interpretation of dental x-rays is time consuming and limited accuracy leads to inconsistent decisions.

**Solution/Product:** Dental Xr.AI is an AI based diagnostic software tool, which provides higher accuracy and consistency (up to 40%). In addition it is time saving, which significantly reduces costs.

**Current Status:** Building the MVP and in parallel a validation study and modeling pipeline are ongoing. Regulatory approval in progress. Management team completed. Negotiations with investors.
AiGnostics: Precision in Computational Pathology.

**Problem:** Manual quantification is time-consuming, leads to inaccurate estimations and observer variability. In addition an ageing population leads to a huge increase in the number of diagnoses.

**Solution/Product:** AiGnostics is an explainable AI software, which identifies cancer cells and non-cancer tissue in histological samples and quantifies features more accurately and faster.

**Current Status:** Building the MVP and growing the data base with over 500,000 annotations. Pilot live at Charité. QM system implementation and test with first potential customer ongoing. Clinical validation and regulatory certification in process. Management team completed and fundraising initiated.

Platform for Accessible and Affordable Healthcare in developing countries.

**Problem:** 1 bn patients in fear of medical impoverishment with insecure income for healthcare providers. 180 bn $ leakage of funds due to corruption (-50%).

**Solution/Product:** Empowering access to healthcare by a mobile health wallet, claim validation and quality assurance. The solution is connecting patient (secure payment), provider (accurate payment) and sponsor (traceable impact).

**Current Status:** Launched in October 2018 in Madagascar. Currently 500+ patients and 150+ babies born in 10 medical centers. Tech development and fundraising ongoing. Regional expansion into Senegal and new verticals. Further team expansion.