BIH Lecture Series | Frontiers in Translational Medicine – Scientific and Structural Challenges

An Industry Perspective

Florian Gantner
Senior Vice President
Translational Medicine & Clinical Pharmacology
Outline

- Translational Medicine
- The dilemma in pharmaceutical R&D
- Biomarkers in clinical drug development
- Use of human biospecimen/Global Regulation on Data Protection (GRDP)
- Industry – Academia collaborations: opnMe.com
Translational Medicine – Scientific Frontiers  
...and some successes

Basic Research
- Diseases
- Genomics, Proteomics, …
- Target discovery
- Compound discovery
- In vitro models
- Animal studies

Translation
- Biomarker
- Mechanisms of Disease
- Disease Positioning
- Patient selection

Clinical Research
- Clinical studies
- Drug intervention
- Patient outcome
Translational Medicine & Drug Development

Translational Medicine: **Integrated application** of
- clinical methods & technologies
- biomarkers
- modeling & simulation
- study designs

- Improve confidence in human drug concepts & candidates
- Understand the therapeutic index in humans
- Enhance cost-effective decision making in *exploratory development* (→ Proof of Clinical Principle-PoCP)
- Increase *confirmatory development* success (→ late stage)

Sustainable and competitive pipeline of innovative products in the best interest of the patients
The pharmaceutical R&D value chain

Discovery → Preclinical Development → Phase I → Phase II → Phase III → Registration

Development Value Chain (7-10 years)

1-2 years → 1 year → 6-9 years

Market

The pharmaceutical R&D dilemma

Lengthy  Costly  Low success
Two dominant questions in drug discovery & early clinical development:

1) Will hitting the target translate into therapeutic improvement?
2) Which patients will respond best (and how can we identify them)?

Two learnings:
1) Mice are not just furry plastic plates
2) Humans are no nude mice
Biomarkers in drug discovery and development: Essential along the entire value chain

- **Discovery**
  - PoCP*
- **Preclinical Development**
  - Biomarker teams established at Lead Optimization start
  - PK/PD analyses
  - Translational biomarkers studies in animals
  - First-in-man studies in HV, safety & tolerability
  - Biomarker exploration & hypothesis testing in man
    - PoCP studies in specified patient populations
    - M&S to inform dosing and population specifics
    - Development of CDx
      - Banking of human biospecimens
      - Exploration of additional indications
- **Phase I**
- **Phase II**
- **Phase III**
- **Registration**
- **Market**

*PoCP = Proof of Clinical Principle, i.e. 'first sign of efficacy'
In other words:
Shift the Development Knowledge Curve…

**Knowledge**

Preclinical | Phase 1-2a | Phase 2b | Phase 3 | Registration

**Time / Money**

Exploratory phase to establish PoCP*  
Desired  
Current

*PoCP = Proof of Clinical Principle, i.e. ‘first sign of efficacy’
Biomarker definition:
A characteristic that is objectively measured and evaluated as an indication of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

Biomarker classification by ‘nature’

- **‘Classic’ Biomarkers**
  - Soluble biomarkers (e.g. plasma, serum, urine, etc.)
  - Blood cell analysis
  - Tissue analysis

- **Genomic Biomarkers**
  - DNA-Sequencing
  - DNA-Methylation
  - RNA-Expression
  - Micro RNA analysis

- **Imaging Biomarkers**
  - Magnetic Resonance
  - Computer Tomography
  - Nuclear medicine modalities
  - Ultrasound
Biomarkers in clinical drug development

1. Understand your drug as early as possible during clinical development:
   - Does a sufficient amount of drug reach the target for the desired period of time?
   - Does the drug bind to the target?
   - Does drug binding elicit a pharmacological effect expected considering the underlying mode of action?
   - Does the drug alter disease pathology?

2. Assess and monitor drug safety:
   - Does the drug (have the potential to) elicit a toxic response before its benefits become clinically evident?

3. Find the right patients:
   - Support diagnosis
   - Include the right patients into the clinical trials
   - Selection of right patients for increased efficacy and/or safety (CDx)
Biomarker Categories (in the BI language)

- **Pharmaco-dynamic**
  - Target Engagement
  - Physiological Response
  - Disease Modulating
  - Outcome Related
- **Safety**
  - On Target
  - Off Target
- **Patient Selection**
  - Diagnostic
  - Risk/Susceptibility
  - Prognostic
  - Predictive
  - ADME
Can the flow of medicines be improved? Fundamental pharmacokinetic and pharmacological principles toward improving Phase II survival

Drug Discovery Today • Volume 17, Numbers 9/10 • May 2012

Paul Morgan¹, Piet H. Van Der Graaf², piet.vandergraaf@pfizer.com, John Arrowsmith³,
Doug E. Feltner⁴, Kira S. Drummond⁵, Craig D. Wegner⁶ and Steve D.A. Street⁷

Three Pillars of Survival:

- Exposure at the site of action over a desired period of time
- Binding to the pharmacological target
- Expression of functional pharmacological activity

An integrated understanding of the above fundamental pharmacokinetic and pharmacodynamic principles determine the likelihood of drug candidate survival in Phase II trials and improve the chance of progression to Phase III.
Non-alcoholic steatohepatitis (NASH): A liver disease of high unmet medical need

Progression of fatty liver disease

- Healthy liver
- Steatosis
- NASH
- Cirrhosis
- Hepatocellular carcinoma

- NASH grading by liver biopsies has several limitations
- Which patients are fast progressors?

39 mio NASH patients
Biomarkers for NASH and Liver Fibrosis:
Liver Biopsy – Grading / Staging & Need for Alternatives

- Biopsy still gold standard for diagnosis and grading of NASH/fibrosis
- Lesions unevenly distributed
- Only a small region assessed
- Sampling errors lead to misdiagnosis/misgradings

Investment in alternative imaging modalities & soluble biomarkers to establish link to clinical NASH grading

Specialized Biomarkers

- **Magnetic Resonance Elastography (MRE)**
  - Provides quantitative assessment of fibrosis in entire liver, but method not readily available
  - TE has potential for patient selection method in clinical trials

- **Transient Elastography (TE)**

- **Oxidative Stress and Apoptosis**
  - Hepatocyte Function
  - Lipids: TG, TC, HDL, LDL
  - Adipokines: adiponectin, leptin, resistin
  - Acute phase reactants: CRP, IL-6, IL-8, TNF
  - Inflammation
  - Fibrosis

Imaging to support therapeutic concepts in IO

Recognizing and killing the tumor by T cells

Tumor Cell Death – Release of Antigens

Imaging T-cell activation

Imaging of TIL presence

FDG: Fluor-Deoxy-Glucose
PET: Positron Emission Tomography
DCE-MRI: Dynamic contrast enhanced MRI
TIL: Tumor-infiltrating Lymphocyte
TME: Tumor micro-environment

Adapted from Chen and Mellman, Immunity 2013
## Nuclear imaging to assess T-cell infiltration and activation

Assess changes in T-cell numbers and T-cell activation

<table>
<thead>
<tr>
<th>In clinical use</th>
<th>[(^{18}\text{F})]_{\text{AraG}} , \text{PET*/CT}</th>
<th>Activated T cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exploratory</td>
<td>[(^{89}\text{Zr})]_{\text{anti-CD8}} , \text{PET*/CT}</td>
<td>CD8(^{+}) T cells</td>
</tr>
</tbody>
</table>
| **Status**      | • IP: CellSight Technologies Inc.  
                 | • PhI/II development on-going |
| **FIH 2017**    | • IP: ImaginAb |

- Explore feasibility of imaging approaches for IO treatment paradigms
- Explore time points best suited for imaging assessment after start of treatment
- Define relevance of observed changes for pharmacodynamic effects, assess predictive value

PET: Positron Emission Tomography
**Genomic Biomarker example in psoriasis:**

Gene-profiling in skin samples of patients

Risankizumab: mAb IL-23 inhibitor

Modulations of
- IL-23 / IL-17 axis
- Epidermal development
- Keratinocyte differentiation
- Epidermal cell differentiation
- Keratinization

Krueger et al., JACI 2015
IL-23 blockade: A new therapeutic option for psoriasis patients

Risankizumab (anti-IL-23 Ab)

Pretreatment

Single dose at 24 weeks

How many patients achieved an "almost clear" (PASI90) or "clear" (PASI100) skin in the 3 dose cohorts?

- Placebo: 0%
- 0.25 mg/kg: 71%
- 1 mg/kg: 83%

Risankizumab/Skyrizi® launched in April 2019
IL-36 receptor regulates the inflammatory response in skin and intestine.
IL-36 R Ab BI 655130/Spesolimab – New Therapeutic Concept for Skin Inflammation

IL-36 and other cytokines

Accessory Protein

IL-36R

IL-36 ligands

(α, β, γ)

NF-κB

MAPK

Spesolimab will:
• Suppress IL-36R activation reducing epithelial cell/fibroblast/immune cell mediated inflammation
• Interrupt inflammatory response that amplifies pathogenic cytokine production
Generalized Pustular Psoriasis (GPP)

Disease Characteristics:
- **Orphan disease, very rare** type of psoriasis, which covers usually entire body
- Repeated, intermittent **acute flares with pustules** and erythema and scaling
- Systemic effects such as high fever, neutrophilia, elevated CRP
- Life threatening and may lead to increased mortality
- Human genetic link: most severely affected GPP patients carry a LoF mutations in natural IL-36 RA

→ **High unmet medical need**
- No approved treatments in US/EU
- No acute flare treatment clinical trials conducted to date
Severity of disease in patient with GPP before treatment

Baseline (before treatment)

Total GPPGA score before treatment

Clear (0)  Almost clear (1)  Mild disease (2)  Moderate disease (3)  Severe disease (4)
Response to treatment in patient with GPP after 1 week

Baseline (before treatment)

Week 1 post-treatment

Total GPPGA score after 1 week

- Clear (0)
- Almost clear (1)
- Mild disease (2)
- Moderate disease (3)
- Severe disease (4)
Response to treatment in patient with GPP after 4 weeks

Baseline (before treatment)

Week 1 post-treatment

Week 4 post-treatment

Total GPPGA score at Week 4

- Clear (0)
- Almost clear (1)
- Mild disease (2)
- Moderate disease (3)
- Severe disease (4)
Efficacy of BI 655130 in Ph2 clinical trial measure in GPPASI*

Mean Percent reduction in GPPASI

Efficacy endpoint

7/7 responders, 5/7 with pustular clearance within 1 week

GPPASI* = GPP Activity Score Index
Spesolimab: First in class potential for various diseases

- Generalized Pustular Psoriasis
- Palmoplantar Pustulosis
- IBD (Crohn’s disease, ulcerative colitis)
- Atopic Dermatitis
Biomarkers are important for clinical drug development:

- Decision criteria, particularly in early clinical drug development
- Acceleration of clinical drug development (e.g. as surrogate endpoints)
- Selection of the “right” patient population
- Supportive in the assessment of an appropriate dose
- Differentiation from competitor drugs
- Assessment of additional indications
- …

Outlook:
- Biomarkers play an increasingly central role in Precision Medicine concepts
Translational Medicine – Structural Frontiers

Basic Research
- Diseases
- Genomics, Proteomics, …
- Target discovery
- Compound discovery
- In vitro models
- Animal studies

Translation
- Biomarker
- Mechanisms of Disease
- Disease Positioning
- Patient selection

Clinical Research
- Clinical studies
- Drug intervention
- Patient outcome
Translational Medicine – Structural Frontiers … and solutions

• GDPR – Global Data Protection Regulation

• Access to and use of Human Biospecimens

• Pharma – academia collaborations: Open Innovation at BI

• …
Data Protection

Art. 1 GDPR Subject-matter and objectives

This Regulation lays down rules relating to the protection of natural persons with regard to the processing of personal data and rules relating to the free movement of personal data.

The dilemma:
• The pharmaceutical industry generates and processes health data
• Health data are considered as a special category of personal data
  ➢ stringent data protection is required
  ➢ the processing of health data is prohibited by default, exceptions
• Art. 9 GDPR Processing of special categories of personal data

1. [...] the processing of genetic data, biometric data for the purpose of uniquely identifying a natural person, data concerning health [...] shall be prohibited.

2. Paragraph 1 shall not apply if one of the following applies:
   • processing is necessary for the purposes of [...] medical diagnosis, the provision of health or social care or treatment or the management of health or social care systems [...]  
   • processing is necessary for reasons of public interest in the area of public health, such as protecting against serious cross-border threats to health or ensuring high standards of quality and safety of health care and of medicinal products or medical devices [...]

Data Protection
Access to human biospecimen and associated data is indispensable for drug development

### Key Points

<table>
<thead>
<tr>
<th>Address</th>
<th>Analyze new scientific hypotheses/verify scientific hypotheses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Explain responder subgroups in clinical trials → high sample number, cross trial</td>
<td>Discover &amp; validate new drug targets or biomarkers</td>
</tr>
<tr>
<td>Identify rare efficacy or safety markers → high sample number, cross trial</td>
<td>Confirm biomarker results in statistically significant &amp; unselected cohorts</td>
</tr>
<tr>
<td>Support companion diagnostics programs and assay development</td>
<td>Enable collaborations: Banked samples &amp; data may open doors</td>
</tr>
</tbody>
</table>
Biobanking at BI

BI maintains a biobank to support the development of innovative medicines. BI’s biobanking activities were first implemented in 2009 by setting up its DNA bank.

Afterwards, BI has expanded its biobanking strategy and infrastructure, also accommodating all other kinds of human biospecimen on a global level.

The BI in-house DNA banking facility has a dimension of 17.4m x 3.6m x 5m and a storage capacity of 5.5 Mio tubes (~500,000 donors).

For other sample species 4 biobanking locations are available at our biobanking service partner. Scalable according to demand.
Corporate Policy: Responsible Use of Human Biospecimens & Associated Data

Human biospecimens are materials taken from the human body, such as tissues, cells, blood, and other bodily fluids. The use of such human biospecimens and associated data has become increasingly important in research and drug development, especially for the understanding of complex, multi-faceted diseases. Such human biospecimen-based research is crucial to the development of new drugs and diagnostic products for the improvement of diagnosis, prevention, diagnosis, intervention, treatment, and cure of diseases.

As an innovative and research-driven pharmaceutical company, Boehringer Ingelheim (BI) makes use of human biospecimens and associated data in current research and drug development programs. BI collects human biospecimens in clinical trials and acquires them from third parties for the purpose of future research. Their responsible use will support more efficient and faster development of new, innovative therapies.

BI is committed to the responsible use of human biospecimens and associated data and will apply high ethical, legal, quality, privacy and data protection standards to all acquisitions, collection, storage and analysis procedures undertaken. Compliance with applicable legal, regulatory and internal provisions is a BI company goal.

Purpose and Scope

Human biospecimens and associated data are exclusively used for research purposes in drug development programs. They are acquired from third parties or collected for specified, tightly restricted analysis in the framework of Biogenponsored clinical trials. Moreover, human biospecimens are also a crucial resource for future. In many cases, they are not yet predictable, medical research purposes. The latter requires compliant collection and long-term storage of biospecimens in so-called banks.

BI recognizes long-term access to human biospecimens and associated data as a vital prerequisite for future medical innovation. BI has adopted an integrated human biospecimen and biobanking framework to assure responsible, compliant and secure collection, long-term storage and access procedures to human biospecimens and associated data.

With this policy BI commits to the responsible use of both human biospecimens and associated data in research and drug development, including strict quality and data protection standards and a responsible biospecimen and data custodianship.

Biobanking

Biobanked human biospecimens and associated data represent an irreplaceable resource for current and future research on health and disease. BI is grateful to the voluntary donation of samples and actively encourages their collection during examinations. As part of the biobanking process, human biospecimens and associated data for unspecified future research use will be collected, processed, stored, analyzed and finally destroyed strictly according to an Information Consent (IC) reviewed by an independent ethical committee at Institutional review board. A quality management system (QMS) certified compliance with relevant human subject and privacy regulations, including EU and German data protection regulations, international and national jurisdictions, ethical principles and other relevant regulations and guidelines.

Appropriate safeguards are in place to protect the donors’ identity and privacy. Human biospecimens and associated data are always coded and BI has no access to any information that may reveal the donor’s identity. Both human biospecimens and associated data are stored in a secure access-controlled environment. Also, their analysis is conducted and regulated by Standard Operating Procedures (SOPs).

Acquisition from third parties

BI research and drug development also requires the acquisition of human biospecimens from third parties, including commercial providers. For any such acquisition BI complies with relevant human subject and data protection regulations, international and national jurisdictions, ethical principles and other relevant regulations and guidelines, including EU and German data protection regulation.

Oversight, Transparency & Dialogue

A Human Biospecimen Science & Ethics Advisory Board has been established to ensure compliance scientific content, quality, legal, data protection and access external ethics expertise. It provides guidance regarding patient-centric, responsible and scientifically sound use of human biospecimens and associated data at BI. In addition, the BI Human Biospecimen Compliance Officer oversees the human biospecimen and biobanking framework on a daily basis.

Human biospecimen research is a dynamic field. BI continues to monitor the international public discourse and constantly review its practices and procedures together with external experts and authorities.

BI is aware of the public dialogue about the responsible use of human biospecimens and associated data and committed towards transparency and high ethical, legal, quality, privacy and data protection standards.
“They did not know it was impossible so they did it” — Mark Twain
opnMe.com - Boehringer Ingelheim’s open innovation portal
Door Opener for Academic Innovators

opnMe.com gives scientists free access to selected, well-characterized pre-clinical tool compounds from Boehringer Ingelheim.

Molecules to Order (M2O) are provided free-of-charge without the need to enter into intellectual property discussions.

Molecules for Collaboration (M4C) invites scientists to submit research proposals to use our unique tools and to find new indications for unmet medical needs.
opnMe.com - Boehringer Ingelheim’s open innovation portal
Door Opener for Academic Innovators

> 1,100 biologists registered from >40 countries
  • Modalities covered: NCEs incl. PROTACs® from the Dundee university, AAV, and Ab

M2O: tools compounds available for free and without strings attached
  • Delivered after only 5 clicks and 5 days to the labs
  • >460 orders and >5,000 compounds shipped worldwide
  • >10 articles cited opnMe including 2 Nature papers using BI tools

M4C: 5 challenges launched
  • >480 proposals received
  • 16 collaborations running or in discussion
  • 1 project already back into the early Research portfolio of BI
opnMe - an OI ecosystem to accelerate collaboratively innovation

opnMe.com is an efficient and reliable Open Innovation portal to foster new ideas
Selection of compounds available for free on opnMe.com to foster independent research

5,000 compounds shipped in 38 countries in 2y
48 tools available within a week with negative control leading to >30 scientific papers

Compounds also shared on thesgc.org
Molecules for Collaboration - overview

- We believe that Boehringer Ingelheim’s unprecedented, high quality molecules shared on opnMe have a great biology potential
- We invite novel proposals for disease research and proposals will be advanced together in collaboration with selected scientists
- Key milestone achieved: One molecule entered Boehringer Ingelheim’s preclinical portfolio

<table>
<thead>
<tr>
<th>Proposals</th>
<th>37</th>
<th>17</th>
<th>215</th>
<th>81</th>
<th>140</th>
<th>116</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collaboration</td>
<td>6</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In Discussion</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

40 *Of the 7, 1 has started as a collaboration in July 2019  
opnMe.com – Molecules for free. Collaborations for Science
opn2EXPERTS – An additional chapter to opnMe.com

**Background**

- Crowdsourcing – Highly efficient to identify original solution to complex questions
- Crowdsourcing brings in 75% of the successful cases a solution from another field of expertise so it means that it is in general quite far from the original field of expertise

**opn2Experts**

- Versatile: Technologies, methodologies, assays, or other precisely formulated questions leading to a mutual benefit
- Allows colleagues to be very precise in their questions much more dedicated to their disease map
- Fast and flexible

**Process**

- opnMe team works with the BI biologists to prepare the question for publication
- Communication via social media (LinkedIn, Twitter), research platforms (Research Gate), direct mail (inospin), web-banners (Nature)

opn2EXPERTS is fast, flexible and dedicated to support innovation

Already 4 challenges online for Inflammation and CNS
Frontiers in Translational Medicine

• Scientific:
  – Lack of disease understanding
  – Lack of understanding of drug candidates
  – Limitations of biomarker applications

• Structural:
  – Data protection regulation
  – Access to and usage of human specimen
  – Disparate interests of industry versus academia
Thanks a lot for your attention!