Translational Research
The bridge between pre-clinical and clinical development

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1. Definition of Translational Research/Medicine (TM)
2. Importance of Translational Medicine
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Definition Translational Medicine (TM)

„Nobody knows exactly what it is, but everyone agrees, that it is important“ (EUSTM Congress, Vienna, 2014)

Translational medicine is a rapidly growing discipline in biomedical research and aims to expedite the discovery of new diagnostic tools and treatments by using a multi-disciplinary, highly collaborative, "bench-to-bedside" approach (Woolf Stephen, 2008)
Definition Translational Medicine (TM)

TM: from bench to bedside with a higher probability of success
Importance of Translational Medicine (TM)

Increasing awareness of TM in academia and industry

Logarithmic increase in number of publications from 1 in 2000 to 4679 in 2013

Randall J Cohrs et al. 2015
Key deliverables Translational Medicine (TM)

- TM encompasses a large number of investigators whose expertise and activities span over the full spectrum of biomedical and associated sciences or disciplines.
- The primary goal is to integrate corresponding findings and capabilities for optimizing patient outcomes, prevention, screening and therapy of disease and improving health.
- The ideal profile of a candidate for TM would be to have a broad range of experience in the field of:
  - Discovery
  - Pre-clinical safety
  - Clinical development
  - Project management
Key deliverables Translational Medicine (TM)

Translational Medicine is all about Biomarker

Biomarker are the heaven of every TM scientist, but not the world!
Definition of Biomarker

“A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to therapeutic intervention”

From
Patient Assessment Biomarkers

- Diagnostic
  - Identify patients with a particular disease

- Prognostic
  - Predict patient’s likely course of disease without therapy

- Predictive
  - Predict a patient’s clinical response to a specific therapy
  - Patient selection
  - May lead to companion diagnostic

Adapted From

Response Biomarkers

- **Pharmacodynamic (PD)**
  - Target engagement
    - Target-proximal biological response
    - Indicates direct drug/target interaction
  - Downstream effects of target engagement
    - Indicates modulation of distal pathways linked to target biology
    - May not be linked to clinically meaningful effects

- **Disease-related (efficacy response)**
  - Indicates modulation of disease pathophysiology
  - May predict disease-related clinical outcome
  - May serve as surrogate for clinical efficacy endpoint

- **Safety**
  - Linked to possible adverse events
  - May be used to identify or avoid safety issues in specific patients

Adapted From

Biomarker Clinical Utility

- Patient inclusion/exclusion
- Patient selection or stratification
- Dose escalation criteria
- PK/PD association
- Decision making especially for proof of biological activity or mechanism
- CDx enabling
- Product differentiation
- Predict or monitor adverse events
- Surrogate for clinical benefit and essential component in adaptive trials
- Exploratory hypothesis generation or testing
- Patient and disease characterization for back translation
Key deliverables Translational Medicine (TM)

• Translate from non-clinical studies and implement pharmacodynamic, target engagement and patient characterization BM in clinical trials

• Provide a breadth of technical and scientific leadership for integration of TR strategies and clinical BM plans

• Develop, outsource and manage clinical biomarker assays including clinical documentation and sample/data management

• Analyze, interpret and model clinical biomarker and patient genomic data and deliver results in a timely manner

• Develop and implement clinical immunogenicity assays for large molecules

• Assess and apply innovative new technologies/methodologies for clinical biomarkers and patient characterization

• Drive development of companion diagnostics
Points to Consider in Translational Medicine (TM)

1. **State** the scientific rationale
2. **Complete** a gap analyses
   “pick the winner earlier”
3. **Implement** and evaluate preclinical models
4. **Establish** and implement a Biomarker (BM) strategy
5. **Nominate** decision criteria
6. **Collaborate**
7. **Evaluate** competitors

**TM = S C I E N C E**

1: first capital of point 1-7
**Future in Translational Medicine**

Traditional Approach in Research

**Bench** → **TM** → **Bedside**

- **Target**
- **Pre-Project**
- **Clinic**

**Traditional Approach in Research**

- **Target ID**
- **1st TV / Assay design**
- **Target decision**
- **HTS assay design**
- **HTS entry decision**
- **HTS**
- **Hit evaluation**
- **Lead-finding**
- **2nd target validation**
- **Pre-project entry decision**
- **Candidate profiling decision**
- **Candidate decision**
- **Phase 1**
- **Phase 2**
- **Phase 3**

**Probability of success in different phases**

- **Phase 1 to phase 2**: 67% / 64%
- **Phase 2 to phase 3**: 39% / 32%
- **Phase 3 to NDA/BLA**: 68% / 60%
- **NDA/BLA to approval**: 86% / 83%
- **LOA from phase 1**: 15.3% / 10.4%

**LOA: likelihood of approval**

Hay M et al 2014
Future in Translational Medicine

- Based on high attrition rates due to lack of efficacy and increasing development costs R+D has to reinvent the innovation process
- How could alternatives look like?
Future in Translational Medicine

- The linear path from target selection to clinical development is limited to known targets.
- The target selection is often based on data of questionable validity (Prinz et al. 2011).
- The process is focused on chemical optimization and not on biological relevance.
- The relevance of pre-clinical models is questionable.
- Drugs usually don’t fail in the clinic because of poor physicochemistry or pharmacokinetic profile (Khana I 2012, Arrowsmith, 2013).
- High attrition rate is caused by insufficient efficacy in >50% of the cases followed by safety concerns (~20%).

Patient Centric Approach (PCA)
Future in Translational Medicine

PCA: Type 2 Diabetes Patient

- Obesity
- Hyperglycemia
- Hypertonia
- Diabetic Nephropathy
- Diabetic Retinopathy
- Increased CV risk
- NAFLD/NASH
- Diabetic neuropathy
Future in Translational Medicine
PCA-what does it mean?

- Get a clear understanding of the underlying pathophysiology of the disease
- Use clinical samples to study your targets by clinical observations, -omics and
- Establish clear go-no-go milestones

PCA approach schematic outline

Raoof A and Aerssens J, 2015
Future in Translational Medicine
PCA-important components and technologies

Raoof A and Aerssens J, 2015
Future in Translational Medicine
PCA-a practical example
Serendipity finding in safety pharmacology
- Some NCEs of a compound class reduced body weight in lean rats without being toxic
- Use of the db/db mouse to demonstrate weight loss

No influence on development of body weight in db/db mice, but decrease in blood glucose

### CPx oGTT after 24 weeks treatment
- 1 g/kg glucose po,
- Fasted glucose mg% pre-, 15, 60 min, after challenge

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Future in Translational medicine
PCA-a practical example: Forward translation

• Meta-analysis of data from COPD patients treated with Roflumilast and co-morbidity T2D
• Clear hints for reduction of fasted glucose in this subgroup of patients
• FORTUNA study: Roflumilast 500µg, 3 month, naive T2D patients 2 arms placebo controlled, double blinded, multi-center study (N=100/arm)

Wouters et al 2012
The meta-analysis and the outcome of the 3 month study in T2D patients with roflumilast had a positive influence on our pre-clinical work. The program was further supported by the senior management. The results supported the level of confidence in the validity and translatability of the pre-clinical results.
Future in Translational medicine

Summary

• Translational Medicine is a discipline of growing importance which is highly demanding
• It requires a deep understanding of the discovery and development process
• Team work and communication is a key success factor
• New strategies have to be implemented to increase the chance of success in our R+D organization
• Be creative and put the patient in the center of your efforts

„At the end you don‘t want to inhibit an enzyme or cure a mouse, it is the patient who matters!“
HP Kley, MD