Potential of Biobanking in Translational Medicine
Arndt A. Schmitz, Bayer Pharma AG

HandsOn: Biobanks 2014, Helsinki, Finland

Conflicts of interest - disclaimer

<table>
<thead>
<tr>
<th>Type</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Employment full time</td>
<td>Bayer Pharma AG</td>
</tr>
<tr>
<td>Ownership interest (stock, patents)</td>
<td>stock holder of Bayer AG</td>
</tr>
</tbody>
</table>

- The organizers provided travel support for this talk, but no remuneration.
- This talk will not detail unapproved therapeutics.
**Translational Medicine**

*Translation* is the process of turning observations in the laboratory and clinic into interventions that improve the health of individuals and the public.

**It is all about getting more treatments to more patients more efficiently.**

**Obstacles along the way can include:**

- Lack of understanding of the science behind the translational process.
- Environments that do not support collaborations in the public and private sectors.
- Inflexible, inefficient clinical trial designs and low participation in studies.

Taken from [http://www.ncats.nih.gov/about/about.html](http://www.ncats.nih.gov/about/about.html)

The National Center forAdvancing Translational Sciences (NCATS) is the newest of 27 Institutes and Centers (ICs) at the National Institutes of Health (NIH). This Center was established in December 2011.

---

**Gaps in Translational Medicine?**

Modified from *Science Translational Medicine* March 24, 2010, issue - C. Bickel, cartoonist
Promise of **Personalized** Medicine

The value of personalized medicine*:

- Ability to make more informed medical decisions
- Higher probability of desired outcomes thanks to better-targeted therapies
- Reduced probability of adverse reactions to medicines
- Focus on prevention and prediction of disease rather than reaction to it
- Earlier disease intervention than has been

**Industry’s incentives:**

- Reduced development time and costs, increased success rates

In 2010 Bayer Pharma decided to implement Personalized Medicine as a key strategic driver in R&D

---


---

Personalized Medicine – even more **complex** than Translational Medicine

**Patients**

From generalized to personalized medicine: "It’s about getting the right dose, of the right drug to the right patient at the right time- based on a refined diagnosis of the underlying disease"

**Regulators**

"Regulatory bodies will demand greater proof of positive patient outcomes to justify approval, reimbursement and price".

**Research and Development**

"Patients can respond differently to the same medicine" (Developing drugs with specific test)
- Pharmaceutical industry
- Biobanks
- Diagnostic Industry
- Academia

**Market Access**

Focused on providing these improved services personalized medicine to each individual patient
- Pricing
- Reimbursement

We at Pharma will only be successful if we deliver innovative, highly differentiated and reimbursable new products

---

Page 6 Schmitz, Bayer Pharma AG - Translation Medicine @ hands on biobanks, Sept. 25th, 2014 Helsinki Finland

Bayer HealthCare
Biobanks help to bridge the gap in Translational & Personalized Medicine

**BIOBANK = ENABLING TECHNOLOGY**

**Necessary**, but **on its own not sufficient**, with many applications:

- Basic Research
- Targets for drug discovery
- **Biomarkers for drug development**
  - Identification
  - Validation
  - Quantification
- **Novel clinical trials**
- New diagnostics

---

**Bad press** for biobanks & biomarker research
In 2008, Bayer Pharma AG established the internal Research Biobank. Its mission is…

- to provide Bayer Pharma scientists with **speedy and compliant** access
- to clinical specimens of standard of care patients
- outside clinical trials
- in particular for biomarker research.

**Our concept**

**in house “xenograft profiling initiative”**

- Pre-Inoculation, Early / Late Tumor → Temporal gene- and protein profiling
- RNAs for gene expression profiling and QPCR; tissues for IHC
- Simultaneous collection of plasma: Biomarker sample acquisition
- Minimized efforts required by exploiting routine experiments 'piggy back'

Initiative provides
- uniform data set by one SOP
- sample sets for follow up experiments
- convenience for next generation of projects
- increased efficiency and productivity
- **compliance** with R3 principle of animal welfare
Research Biobank provides healthy control samples for BM characterization

**Question:** impact of preanalytics?

**Concept:** obtain healthy control blood samples

**Actions:** since 2009 together with in house ph I unit under approval by local IRB

- longitudinal (1, 2, 3, 4, 8, 12 weeks)
- circadian (7, 10, 13, 16 hrs)
- serum, EDTA, citrate, Hep-plasma
- aliquoted on MTP ready to go

Preanalytic Initiative:
Addressing two common handling errors

- **Mislabelling and processing delays** of samples can have significant impact on the trueness of biomarker measurements
- Going beyond documentation: Can we "ask" the samples themselves?
- beta-Test of a metabolomics-based plasma quality control assay

- **1st test - mislabelling**
  - We send them 40 samples blinded.
  - There were 10 from each of 4 types.
- **All our 40 blinded samples were assigned correctly.**
Preanalytic Initiative: Addressing two common handling errors

- **2nd test – Processing delays**
- Next, samples were "mistreated" to mimic deviations from preanalytical SOP.
- 120 samples with pre-analytical variation:
  - Correct: freeze plasma from blood within 1 hr.
  - OR: delays of 6, 12, 48 hours till freezing.
  - OR: 4 freeze-thaw cycles -80/+4C.
- Blinded analysis of samples:
  - assigning quality control score, range 0 to 100.
- **RESULT**: 109/120 correct (QC score > 90).
- **USE WHERE MATRIX/TIMING IS CRUCIAL**;
  - OR TO MONITOR SITE/TRIAL PERFORMANCE
- Only 100 µl volume required

Success factor: partnering concept

- **CROs**
  - sample 'procurement'
  - clinical data
  - sample processing & analytics
- Risk = unclear relations =>
  - define clear terms (ethics, business and science)
- **clinicians**
  - specimen 'generation'
  - clinical data
  - interpretation & publication
- **patient:**
  - hope for new treatments
- **Bayer**
  - sample processing
  - sample analytics
  - interpretation & publication
- **Success** = partnering =>
  - dialog to identify common interests / individual needs

Page 13 - Schmitz, Bayer Pharma AG - Translation Medicine @ hands on biobanks, Sept. 25th, 2014 Helsinki, Finland

Page 14 - Schmitz, Bayer Pharma AG - Translation Medicine @ hands on biobanks, Sept. 25th, 2014 Helsinki, Finland
Obtaining samples of routine care

CRIP - Central Research Infrastructure for molecular Pathology @ Fraunhofer Institute, Potsdam, Germany

CRIP - Central Research Infrastructure for molecular Pathology @ Fraunhofer Institute, Potsdam, Germany

hospital biobanks

recoding by CRIP „broker”

sample requestors such as us

Criteria for assessing biobanks

This contest evaluated biobanks based on:

1) Quality (material and operations)
2) Transparency (outreach activities and donor relations)
3) Usage (sample turnover)
4) Connectivity (integration into biobank networks and trans-institutional infrastructure)
5) Innovation (innovative solutions for any kind of biobank-related problems)
6) Sustainability (outline of business model)

WE WOULD ADD
- Availability of relevant samples
- Legal aspects (PI/IC)
Results of a donor survey

10 multiple choice questions were distributed in regional dermatological practices (patients) and among medical students (probands) => snapshot of local community (n = 619)

Would you agree that the samples may be used for further currently not defined research purposes?

<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>Yes</th>
<th>Total (100%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>101</td>
<td>440</td>
<td>541</td>
</tr>
<tr>
<td>(%)</td>
<td>18.7%</td>
<td>81.3%</td>
<td></td>
</tr>
</tbody>
</table>

Would you agree with genetic studies of the samples?

<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>Yes</th>
<th>Total (100%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>129</td>
<td>411</td>
<td>540</td>
</tr>
<tr>
<td>(%)</td>
<td>23.9%</td>
<td>76.1%</td>
<td></td>
</tr>
</tbody>
</table>

A smaller proportion of the higher educated agrees with the usage of the samples for currently not defined scientific questions (p=0.0241).

⇒ We need better education of the broad community on biobanks, biomarker, and medical research!

„How to get samples out?“ (access rights)

Samples are binned based on their value
Criteria for ‘value’ have been defined.

Three-tiered decision tree for access:
Request’s value is judged by biobank staff, based on defined criteria.
In case of conflict, escalate to colleagues / to management.

- no restrictions release also for method development
- special samples access restricted to particular project
- use restricted to scientific project work by established analysis protocol
- => several
- => vast majority
- => exception
Success Factor: Standardization

Aliquoting (done by SOP) increases value of specimen!

Resected human specimens:
- tumor tissue sample
- adjacent normal tissue sample

mRNAs -> QPCR
proteins -> ELISA
slides -> IHC

mRNAs -> QPCR
proteins -> ELISA
slides -> IHC

The clinical data PLUS the sum of all experimental data generate innovation for the patients.
Biomarker concepts in Pharma Drug Development

- **Prognostic biomarker**: predict the natural course, indicating whether the outcome for the patient is likely to be good or poor (prognosis)
- **Predictive biomarker**: help the doctor to decide which patient is likely to benefit from a specific treatment, e.g. oncogene mutation
- **Pharmacodynamic biomarker**: help to decide what dose might be most effective

Thus, biomarkers have the potential to change drug discovery and medicine!

→ **Personalized selection of a drug**: personalized medicine

---

Biobank sample needs for...
Research on **prognostic** biomarkers

BM research for prognostic BM – provide evidence that

BM is measurable in relevant humans (requires **human samples** from standard of care patients in defined indication) AND
BM molecular data **correlate** to **clinical data** to provide additional insight

Example – amount of circulating tumor DNA correlates to metastasis in CRC (own data - T. Gorges et al., 2012)

NOTE - no **therapeutic** directly involved
Biobank sample needs for…

**Pharmacodynamic** biomarkers

BM research for pharmacodynamic (PD) BM – provide evidence

- BM is regulated by our *therapeutic* in relevant *animal* model
  (requires samples from pre/post dosing in vivo model)

AND

- BM is measurable in relevant *humans*
  (requires samples from patients from standard of care in planned indication of *therapeutic*)

---

**Stratification** biomarkers

BM research for stratification BM – provide evidence

- Level of BM is correlated to efficacy of our future *therapeutic* in relevant *animal* models
  (requires samples from pre dosing in vivo models and outcome data)

AND

- BM is measurable in relevant *humans*
  (requires samples from patient from standard of care patients in planned indication of future therapeutic)

AND

- **Assay** by which BM is measured
  - can become companion diagnostic.
Biobank sample needs for...

Biomarker **Assay** development

- need: biological reference materials for ELISA assay development
- solution: prospective study, local network facilitated by key opinion leader
- delivered: 15 x 1 ml plasma aliquoted at site of each of total 30 cancer patients with low / medium / high BIOMARKER levels
- requirements: ethics vote, contracts, patient informed consent, logistics, site visits…

Similarly – tumor sections with Affymetrix global expression profile annotated
Similarly – tumor sections with defined deviations from fixation protocol for robustness

=> These sample requirements go beyond those of classical biomarker research.
=> These analytical requirements go beyond the "expert center" concept, where the samples are analyzed on site and only data reported.
=> However, also these data could be reported back to biobank.

---

Biobank sample needs for...

**Evaluation** of BM laboratory services

testing novel molecular services of US biotechs using German reference labs for concordance, eg using clinical KRAS info for NGS evaluation

NEW: global pharma trials - need samples for transferring assays from US biotechs to CROs operating in Asia/Pacific
Again, both uses go beyond „expert center” concept
Access to historic clinical specimens of clinical trial participants

In clinical trials of new therapeutics in solid cancer indications, access to historic FFPE material of trial participants requested

• to perform eg IHC for stratification
• to perform eg NGS for Biomarker discovery

This requires

• access to these samples (= performance of healthcare systems)
• Informed Consent of participants (= society inclination towards genetics).

Global phase III trials allow us to assess these two aspects in several countries.

Limited access to historic FFPE material

phase III trial (n > 400):
possibilities for onco genomics

From > 700 participants, > 400 had samples available. Of these, 5 from 6 consented to onco genomics analyses. However, only from 1/3 a FFPE block was available to us. (Phase III trial results 2013)
Monitors inquired with sites why samples were not available

Reasons given for not sending tissue samples:

Some reasons Bayer cannot remedy
- No tissue or not enough tissue ("previously used for other studies"); "pt performed 3 lines of chemotherapy before THIS TRIAL"); "too small" even for 3 slides; cytology specimen only)
- "Country not taking part in any tissue analysis"
- "Countrywide general big prejudice to these type of testing (taking additional samples, sending them to a foreign country…) …due to some previous events"
- "State health authority is not in favor of exportation of tissue sample, so institutions barely do that part for clinical trials"

Other reasons may be addressable
- Sample at a different site
  - "sample is held at a different hospital and nurse is having difficulty requesting it"
  - "patient came from another hospital so no tumor block available at this site"
  - "As the surgery was performed in a city far from the site it is not possible for the patient to go and fetch the tumor block"
  - "PI relation with the external laboratory very difficult"

Potential consequences of limited access to historic FFPE samples in our trials

Be aware of societal issues with tissue donation / genomic analyses. If this is deemed crucial for the trial, might influence country participation.

Be aware of site to site differences within a country regarding readiness to grant access to historic tissues. If this is deemed crucial for the trial, might influence site participation.

Same holds true for site to site differences re technical quality / usability of samples.

On the long run – liquid biopsy concept implemented? Till then – thank you for your support in this matter!!!

=> Biobank experience can be enabling technology for clinical trials.
Summary

**Stakeholders** in translational and personalized medicine need to connected by strong **bridges**.

**Biomarkers** can provide scientific rationale for better **therapeutics**.

**Biobanks** can be an enabling technology for biomarker activities and for more molecularly oriented **clinical trials**.

---

**Thank you!**

Acknowledgements:
Patients and their clinicians and nurses;
Bayer Biomarker management team, fellow scientists, lab staff;
external partners at biotechs and CROs.
Forward-Looking Statements

This presentation may contain forward-looking statements based on current assumptions and forecasts made by Bayer Group or subgroup management.

Various known and unknown risks, uncertainties and other factors could lead to material differences between the actual future results, financial situation, development or performance of the company and the estimates given here. These factors include those discussed in Bayer’s public reports which are available on the Bayer website at www.bayer.com.

The company assumes no liability whatsoever to update these forward-looking statements or to conform them to future events or developments.