The Promise and Reality of Biomarkers in Pharmaceutical Development

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NewMedicines

UCB

Christen, living with Parkinson's disease
The Promise and Reality of Biomarkers in Pharmaceutical Development

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The Weight of Expectation:
Can Translational Medicine and Biomarkers ‘rescue the pharmaceutical industry’ from R&D costs and attrition?

The challenge…
Dr. Timothy Anderson of Bernstein Research looked at the prospects for nine major pharmaceutical companies to 2020. His June 16 investor note found some companies with good long-term prospects from existing products, while others fall off the "patent cliff" as generic competition is expected to pound their sales.

90% Attrition in Pharmaceutical Clinical Development: What a Waste!

Only 10% of medicines make it through from Phase I clinical studies to Launch.

40% of the failures are occurring in Phase III - the most expensive stage.

At least 30% is due to lack of efficacy.

“It is not necessary to change. Survival is not mandatory.”

W. Edwards Deming

Ismail Kola & John Landis

*Nature Reviews Drug Discovery 3, 711-716 (August 2004)*
Biomarker utility throughout the pharma pipeline

From early decision making to diagnostics

Biomarkers? Applied to us…

A measurement made on a body tissue, fluid or excretion to give a quantitative indication of

• Exposure to an active substance, and/ or
• Change in disease activity
• Compound safety

1/ Enabling project go/no go decisions
2/ Candidate diagnostics
Embedding biomarker science in drug development and clinical practice

The Pharmacologic Audit Trail
Pharmacologic Audit Trail*

Is the target present in the disease tissue?  
*Target validation/ translational biology*

Is an appropriate exposure of the drug possible in the tissue?  
*Pharmacokinetics*

Does the drug bind/occupy the target in the right tissue?  
*Target Occupancy*

Does the engaged target/drug complex create a detectable, proximal and specific downstream event in the disease tissue?  
*Target Engagement*

Is there a disease or pathway event, distal to the target, impacted by the engaged target?  
*Biological Effect*

Beyond the biomarkers, is there a clinical effect?  
*Clinical Endpoint/Surrogate endpoint*

*Adapted from Collins, I and Workman, P.  Nature Chemical Biology 2:689-700, 2006*
Can the flow of medicines be improved?

Fundamental pharmacokinetic and pharmacological principles toward improving Phase II survival

Drug Discovery Today Volume 17, Issues 9/10 2012 419 - 424

Definition of the three Pillars of survival

For a development candidate to have the potential to elicit the desired effect over the necessary period of time, three fundamental elements need to be demonstrated:

1. Exposure at the target site of action over a desired period of time
2. Binding to the pharmacological target as expected for its mode of action
3. Expression of pharmacological activity commensurate with the demonstrated target exposure and target binding
Figure 1  Risk management matrix, based on three Pillars of survival, for use in clinical development to assess likelihood of testing the mechanism and program progression.

Can the flow of medicines be improved? Fundamental pharmacokinetic and pharmacological principles toward improving Phase II survival

Drug Discovery Today Volume 17, Issues 9?10 2012 419 - 424

FIGURE 2
Alignment with three Pillars of survival for 44 Phase II programs between 2005 and 2009 in the Pfizer dataset.

Drug Discovery Today
Biomarker Hierarchy

Building ‘reasons to believe’

No one single biomarker/assay can answer all the questions. As we move through early development confidence is built by biomarkers of varying and increasing utility.
Target Engagement

- A target engagement biomarker must be
  - Proximal to the target
  - In the disease pathway
  - In the disease tissue
- A target engagement assay must be
  - ‘Fit for the clinic’
  - Sufficiently validated for a meaningful readout in the Phase1 (patient) study
    (it may not always be possible to make the assay truly quantitative for dose selection)
Target Engagement

Why is it so important?

*Only when we have measured target engagement can we be confident we have adequately tested the mechanism of a drug’s activity in a disease.*

Can sufficient engagement, to deliver an effect, be achieved at well tolerated doses?

**Drug has no/weak clinical effect and no (or insufficient) target engagement**

→ Not surprising - new molecule needed

**Drug has no/weak clinical effect and full (or sufficient) target engagement**

→ Concept flawed - do something else
The impact of biomarkers throughout drug development

From early mechanistic studies to diagnostics

Basic research → Target validation → Lead Discovery → Candidate selection → First in Human → Proof of Concept → Full Dev → Market

Experimental Medicine and Diagnostics

Real world examples:

- Target Engagement in Immunology
- Target Occupancy in Neuroscience
- Biomarker data to make early decisions
- Biomarker robustness and utility
- Patient diagnostics and stratification
Target Engagement

Immunology example

DeOnna, living with rheumatoid arthritis
Target engagement – Inflammation example
A quick introduction to a kinase inhibitor for immune disease

...an orally active, small molecule to treat autoimmune disease(s)

Predominantly an immune cell signalling molecule

Inhibition will reduce cell growth and activation

Inhibition will increase apoptosis (cell death)
Target engagement – Inflammation example

The Ideal Target Engagement Biomarker?

Kinase activity

\[ \text{AKT} \stackrel{P}{\rightarrow} \]

Various effects inc:

- Cell Activation
- Cell Growth
- Cell Death

The challenge of Target Engagement is to identify markers which are modulated specifically and robustly by the target in an accessible cell-type or tissue using an assay which can be readily used in clinical studies.

Can we measure?

If not how close can we get?
Target Engagement – Inflammation example

Drug inhibition of a kinase activity and downstream phosphorylation changes in psoriatic tissue

Significant investment in time and effort in candidate biomarker assessment:

Ideally- start 2 years before FIH

Staining of lesional and non-lesional skin sections from psoriatic patient

Target Engagement

• Proximal to the target
• In the right disease pathway
• In the right tissue/cell

“Get closer ... get in disease...get in tissue”
Prof Chris Chamberlain, VP ExpMed and Diagnostics, UCB
Target engagement – Inflammation example

What can we achieve in healthy volunteer FIH studies?

Target Engagement =
- Proximal to the target
- In the disease pathway
- In the tissue

Achievable in healthy volunteers?

Induced biological effect

*Ex vivo* stimulation of blood with anti-IgE promotes degranulation of basophils. A kinase dependent mechanism

Need to get into disease tissue asap. For this kinase project, the top dose was performed in psoriatic patients to enable phospho-protein immuno-histochemistry in disease tissue.
Induced Biological Effect – Inflammation example

Validation data for the assay in ex vivo challenged healthy volunteers

Inhibition of anti-IgE triggered Basophil

<table>
<thead>
<tr>
<th>% Inhibition of CD63+</th>
<th>Donor 1</th>
<th>Donor 2</th>
<th>Donor 3</th>
<th>Donor 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC50</td>
<td>74.53</td>
<td>141.2</td>
<td>112.1</td>
<td>39.66</td>
</tr>
</tbody>
</table>

Validation Number: SG003/2013

Basophil Degranulation Assay
Method Validation Report (Final V0)
Induced Biological Effect – Inflammation example

Seasonal effects necessitate a rapid assay rework and validation

- Assay ‘fit for clinic’ validation run in June/July – peak pollen season
- However, there appeared to be a drop in basophil counts in all individuals- allergic and non-allergic

 Expect the unexpected-this is science!


Circulating basophils in normal subjects and in subjects with hay fever.

Hirsch SR, Kalbfleisch JH.

“…the nonatopic group also showed a significant elevation of basophils during the ragweed season,”
Target Occupancy

Neuroscience example

Sten, living with restless legs syndrome
Target Occupancy – Neuroscience example

Positron Emission Tomography (PET)

Positrons are subatomic particles produced by certain isotope-radionuclides e.g. $^{18}\text{F},^{11}\text{C}$

Positrons have a $+\text{ve}$ charge and when they collide with an electron, the 2 particles are annihilated

The resultant energy is emitted as 2 photons moving in opposite directions

The 2 photons can be detected by an array of photosensitive cells

Radial arrangement of these cells allows computer analysis of source

3D picture constructed of location of positrons and hence radionuclide
Target Occupancy – Neuroscience example
PET Imaging

What do we need to establish a CNS PET study?

A candidate drug molecule
An molecule targeted at inhibiting/modulating a key neurological protein, implicated in disease

AND

A PET tracer
A molecule able to bind to that key neurological protein, labelled with a isotope-radionuclides e.g. $^{18}$F,$^{11}$C. This molecule must be capable of being displaced by the drug
Target Occupancy – Neuroscience example

Labelled PET tracer binding before and after administration of a neurotransmitter receptor inhibitor

Baseline:
PET tracer bound to neurotransmitter receptor

Increasing dose of neurotransmitter receptor antagonist
At the highest dose the drug blocks the receptor for the PET tracer, indicating 100% target engagement of the neurotransmitter receptor in the brain.
# The Pharmcological Audit Trail - Summary

**Building ‘reasons to believe’; de-risking later phase development**

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target Engagement Biomarker</td>
<td>Measure a proximal downstream effect in the disease pathway and in the disease tissue</td>
</tr>
<tr>
<td>Target Occupancy</td>
<td>Measure binding to the target Mode of Action in the target tissue</td>
</tr>
<tr>
<td>Biological Effect</td>
<td>Measure an effect associated with the target mechanism; maybe unrelated to the pathway</td>
</tr>
<tr>
<td>Induced Target Modulation</td>
<td>Measure an effect associated with the target mechanism; maybe unrelated to the pathway following <em>ex vivo</em> induction</td>
</tr>
</tbody>
</table>
Two Potential ‘Pit falls’

1/ Delivering data you can rely on

The place of exploratory statistics
Are the results reproducible?

Sometimes even the placebo yields a positive readout.

“Make sure to take it every day, otherwise the effect wears off.”

At 12 weeks, 10-20% RA patients treated with placebo are classified as responders.
Exploratory statistics are critical in biomarker analysis

*Bringing quantitative thinking to early drug development*

Statistical support for the design, analysis and interpretation of clinical trials, and pre-clinical experiments

Reproducible result or Random variation?

- Impact of variability
  - Can we answer the key objectives of the study?
- Probability of Success
  - What conclusions can be drawn from the data
  - Optimal statistical methodology
  - Quantitative go/no go decision criteria
  - Quantification of risk
  - Appropriate design
Robust decision making: Defining biomarker study success

Need to pre-specify clear success criteria

- Lets look for a hint of efficacy
- Lets look at the mean values
- A trend will be sufficient
- I’ll know it when I see it
- Let’s use the balance of probabilities to decide

Whatever rule we use, there are two sorts of errors we can make:
- Mistakenly stopping a good drug
- Mistakenly continuing with a bad drug (i.e. results not reproducible)
Example of an fictional small biomarker study

True responder rates of: Placebo: 30% Active: 45%

Imagine we run a small study of 10 per group, then:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Probability</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responder rate is higher in the active group</td>
<td>68%</td>
<td>✅ Progress a good drug</td>
</tr>
<tr>
<td>Responder rates are equal or less in the active group</td>
<td>32%</td>
<td>❌ Stop a good drug</td>
</tr>
</tbody>
</table>
Two Potential ‘Pit falls’

2/ Biomarker assay robustness

The place of sample quality
Assay Characterization & Qualification: What are you really measuring?

“It is only a biomarker if you can measure it...robustly!”
Dr Suzy Rigby, Head of Bioanalysis, AstraZeneca 2003

Assay Characterization
Assessing the technical performance of an assay (characterization)
Measurement of analytical performance characteristics
Determining conditions when the assay gives reproducible & accurate data
Assay performance/characteristics in human samples

Qualification
Linking biomarker to biological processes
Linking biomarker to clinical endpoints
Assessment inter & intra patient variability along with sensitivity to change

The degree of rigor depends on intended use
Different analytes (biomarkers) vary in their robustness and sensitivity to handling.

<table>
<thead>
<tr>
<th>Freeze-thaw cycle</th>
<th>pg/mL</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>bFGF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>116</td>
<td>100</td>
</tr>
<tr>
<td>1</td>
<td>177</td>
<td>153</td>
</tr>
<tr>
<td>2</td>
<td>185</td>
<td>159</td>
</tr>
<tr>
<td>3</td>
<td>202</td>
<td>174</td>
</tr>
<tr>
<td>Soluble Flt-1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>90</td>
<td>100</td>
</tr>
<tr>
<td>1</td>
<td>111</td>
<td>124</td>
</tr>
<tr>
<td>2</td>
<td>121</td>
<td>134</td>
</tr>
<tr>
<td>3</td>
<td>124</td>
<td>138</td>
</tr>
<tr>
<td>PIGF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>15</td>
<td>100</td>
</tr>
<tr>
<td>1</td>
<td>15</td>
<td>103</td>
</tr>
<tr>
<td>2</td>
<td>16</td>
<td>111</td>
</tr>
<tr>
<td>3</td>
<td>16</td>
<td>111</td>
</tr>
<tr>
<td>VEGF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>242</td>
<td>100</td>
</tr>
<tr>
<td>1</td>
<td>362</td>
<td>150</td>
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<tr>
<td>2</td>
<td>473</td>
<td>196</td>
</tr>
<tr>
<td>3</td>
<td>504</td>
<td>208</td>
</tr>
</tbody>
</table>

Plasma subjected to 3 freeze-thaw cycles shows unaltered analyte recovery for PIGF*...but not for bFGF, soluble Flt-1, and VEGF.

*The concentrations shown are the mean value of three replicates. Recovery is calculated as percent of cycle 0 (fresh).
Sample Quality is ‘King’:
True donor-to-donor differences can be masked

Gene expression profiles from similarly processed PAXgene preparation

Donor A: 1 week frozen vs Donor B: 26 weeks, frozen

Donor A: 2 hrs ambient vs Donor B: 24 hrs ambient
Patient stratification and diagnostics
The people who take our medicines…
...are all different – races, gender, ages…

...and all are different in how they respond to a drug and metabolise a drug
The drugs don’t work…well not on everyone

Cost of treating chronic illness in the UK - £7 out of every £10 spend on healthcare.  (source: Dept. of Health)

In many of these chronic illnesses more than 50% of patients do not gain benefit from the drugs available
Percentage of the patient population for which a drug is ineffective

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANTI-DEPRESSANTS (SSRIs)</td>
<td>38%</td>
</tr>
<tr>
<td>ASTHMA DRUGS</td>
<td>40%</td>
</tr>
<tr>
<td>DIABETES DRUGS</td>
<td>43%</td>
</tr>
<tr>
<td>ARTHRITIS DRUGS</td>
<td>50%</td>
</tr>
<tr>
<td>ALZHEIMER’S DRUGS</td>
<td>70%</td>
</tr>
<tr>
<td>CANCER DRUGS</td>
<td>75%</td>
</tr>
</tbody>
</table>

Source of data: Brian B. Spear, Margo Heath-Chiozzi, Jeffrey Huff, “Clinical Trends in Molecular Medicine,” Volume 7, Issues 5, 1 May 2001, Pages 201-204
Alignment of drug and diagnostic development is challenging

Drug development
- Phase I
- Phase II
- Phase III
- NDA

Diagnostic development
- Development must be in parallel to drug development

Example in immunology:

**Severe asthma**
Xolair (Anti IgE for severe asthma) prescribed using IgE level to determine dose
FDA Draft guidance – in vitro companion diagnostic devices (July 2011)

Generally, if safe and effective use of a therapeutic depends on a diagnostic, then FDA will require approval or clearance of the diagnostic at the same time that FDA approves the therapeutic.

Very challenging but it is anticipated that most specialist therapies in 2020 will include companion diagnostic as key component (PwC)
The Promise and Reality of Biomarkers in Pharmaceutical Development:
Conclusions and Summary
Pharmaceutical companies have a lot resting on the success of translational medicine and biomarker approaches.

Following the ‘pharmacological audit trail’ is critical for an early project.

De-risking later development by insisting on demonstration of target engagement will have a significant impact.

The ‘pitfalls’ of poorly powered studies and poor sample handing are better understood; assay qualification standards are developing fast.

There is broad recognition of biomarker utility in the pharmaceutical industry: from early decision making to patient stratification.

The world is watching…and expecting biomarkers to deliver!
Acknowledgments

All my colleagues in UCB (and former colleagues in AZ and friends in other Pharma) who have challenged me in how we deliver biomarker driven-decisions to early development and ultimately new medicines to patients.
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