Basics of Translational Medicine

Biomarkers: An essential element of developing new medicines

John Beaver
Biogen Community Lab
16 December 2020
Overview

• How did I become a drug developer?

• What a crazy business: Why do investors give biopharma $$$ if they usually lose it all?

• What are biomarkers and are they any good for developing new medicines?

• Let’s bring this to life with some examples
**Experience**

- **Biogen**
  - 4 yrs 7 mos
  - Vice President & Head, Biomarkers Center of Excellence
  - Full-time
  - Oct 2016 - Present • 4 yrs 3 mos
  - Senior Director, Global Biomarker Discovery and Development
  - Jun 2016 - Sep 2016 • 4 mos

- **Aires**
  - 2 yrs 1 mos
  - Site Director, Global Biomarker Discovery & Development
  - Full-time
  - Feb 2015 - Nov 2016 • 2 yrs 3 mos

**Education**

- **University of Cambridge**
  - PhD
  - 2003

- **Rutgers, The State University of New Jersey-New Brunswick**
  - BA with High Honors
  - 1998

**Skills & Endorsements**

- **Take skill quiz**

**Drug Discovery**

- Endorsed by Emilio Merlo Pich who is highly skilled at this
- Endorsed by 4 of John's colleagues at Biogen

**Biomarkers**

- Endorsed by Emilio Merlo Pich who is highly skilled at this
- Endorsed by 3 of John's colleagues at Biogen

**Recommendations**

"John is one of the brightest scientists I have worked with. He has a great understanding of the principles and application of imaging to neuroscience and drug discovery. He has a clarity of..."

- **Eugeni A. (Ilan) Rabiner**
  - Executive Vice President, Head of Translational Applications at Invivco, LLC
  - February 13, 2013: Eugeni A. (Ilan) managed John directly

**Accomplishments**

1. **HONOR & AWARD**
   - Presidents Award
   - Abbie

27. **PUBLICATIONS**
   - Determination of detection sensitivity for cere...
   - NMR in Biomedicine

**Contact**

- Your Profile
  - https://www.linkedin.com/in/john-beaver
How did I become a drug developer?

4.5yrs @ Biogen

This is my brain!
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What a crazy business: High Risk Enterprises Face Unique Challenges

OIL & GAS

Challenges

If I can even get the claim: Does the claim hold oil? Can I reach it? What new technology will be needed to do so? What will it cost to get it out? Will the price of oil be high enough to turn a profit when I do? ....

PHARMA & DIAGNOSTICS

Challenges

Does the target play a critical role in the disease? What questions do we need to answer to understand this role? Can we design a molecule to interact with the target? Can we get it to the target? Is it safe? Does it do what we want it to do when it hits the target? Is the impact meaningful? Will it be reimbursed? ....

FILM INDUSTRY

Challenges

Can I successfully market the product before shooting even the first frame? Can I afford the minimum investment ($60M-$200M) to guarantee success for content production? Can I get it done in time and without any actors getting hurt (or worse)? Can we secure distribution channels? ....

Biogen
The Rewards and the Failures can be Staggering

**OIL & GAS**

- **Examples**
  - 2013: Royal Dutch Shell Pulls out of Chukchi Sea $4.1B loss
  - 2016: Discovery of Wolfcamp Formation, TX Shale Deposit (est. 900B bls)

**PHARMA & DIAGNOSTICS**

- **Examples**
  - 2006: torcetrapib (Pfizer) Kills P3 due to safety est. loss $800M

**FILM INDUSTRY**

- **Examples**
  - 2013: 47 Ronin $250M production budget. Est loss $150M
  - 1939: Gone with the Wind <$4M production budget. 2014 ROI >$3.4B
Bringing New Medicines to Patients Demands a Successful Business Able to Overcome Immense Challenges

- Do I understand this biological mechanism?
- Can I create the right molecule to manipulate this mechanism?
- Is my molecule safe to administer at all?
- When administered (and how, exactly, do I do that?), how much should I give and does it reach the target?
- Did enough of it get there and stay there for long enough? Is it still safe at that dose?
- Did I give it to the right patient?
- Does it have the desired clinical effect, and did I look at the right time?
- Does it cause a meaningful change in disease course?
- Will prescribers prescribe it and will payors pay for it?

We Must Convince:
- Ourselves
- Our Investors
- Regulators
- Patients
- Prescribers
- Payors
Risky Business

9-15 years with average costs of $2.6B (2013)
Back of the Envelope Calculation:

What are the chances of a new drug becoming a medicine for patients?

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Probability of Success can be increased by addressing key questions with biomarkers

**Target Selection**
- Do I understand this **biological mechanism**?
- Can I create the **right molecule** to manipulate this mechanism?
- Is my molecule **safe** to administer at all?
- When administered (and how do I do that?), does it **reach the target**?
- Did **enough of it** get there and stay there for long enough?
- Did I give it to the **right patient**?
- Does it have the **desired clinical effect**, and did I look at the right time?
- Does it cause a **meaningful change in disease course**?
- Will **prescribers prescribe it** and will **payors pay for it**?

**Biological Profile**

**Hit ID & Lead Op**

**DC Selection**

**R2D**

**IND**

**Ph I**

**Ph II**

**Ph III**

**NDA**

**Ph IV**

**Pharmaco-Dynamic**

**Clinical**

**Safety**

**Biomarker Applications**
So, what is a biomarker anyway?

A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or biological responses to a therapeutic intervention.
Biomarkers in drug development
Focus on Targets, Technologies, Translation

Avoid going ‘blind’ into clinical studies

- **Target engagement**: Does the medicine reach the intended target(s)?
- **Patient Stratification**: Which patients will benefit from the medicine?
- **Dose Selection**: What is the minimum dose required to occupy the target?
- **Mechanism**: Does binding the target elicit a relevant physiologic response?

Biomarkers – Imaging, Electrophysiological, Biochemical, Behavioral, PGx
Overview

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Images effectively communicate medical science

Most science is communicated via graphs, charts and plots

- Difficult for non-experts to understand the key message
- Typically lack visual impact

Medical images can show directly and clearly the effect of a treatment on disease

- Most people have had previous exposure to medical images and can understand their message (e.g., Xrays for bone fracture)
Example: GSK’s drug Alli

- GSK launch of weight-loss drug Alli in Europe
- Used medical imaging to change the public’s perception of Alli from a ‘vanity drug’ (i.e., a slimming tablet) to a medicine with a clear health benefit
  - Provided scientific evidence of health benefits in a way the public could easily understand
  - Strategy: a small Magnetic Resonance Imaging (MRI) study individuals to visualize Alli’s effects on fat related to health risks in overweight/obese individual
  - Cost: ~$250k USD
  - Product launch was highly successful across EU, supported by extensive press coverage of MRI study showing Alli’s impact on ‘toxic fat’

Daily Mail front page coverage of GSK’s study (UK’s highest circulation daily)

“...these subjective feelings are borne out by scientific evidence using state-of-the-art MRI scans - the cause of his newfound energy and improved mood literally caught on camera. What these scans reveal is the astonishing amount of visceral fat David has shed.”

“Dr Haslam points to David Smith’s example to show how quickly we could all turn our health around in this way. ‘There’s no doubt that with a BMI of 36, David’s health was at risk - and yet within three months his life expectancy will have improved dramatically.’
Pharmacotherapy for obesity

Alli (Orlistat 60mg) is a medicine for weight loss

alli – your new partner in weight loss
Body Mass Index is a poor predictor of disease risk

Visceral vs Subcutaneous Fat Deposits

- Visceral adipose tissue (VAT) and intramuscular adipose tissue (IMAT) have more profound adverse health effects than subcutaneous fat
- Insulin Resistance, Chronic inflammation, Oxidative Stress, Coronary Disease

“[Sumo wrestlers] have low cholesterol, they have low insulin resistance and a low level of triglycerides," said Bell. "Their fat is all stored under the skin, on the outside."*  


*Associated Press, 2007
Hepatic Steatosis (Liver fat)

Fat accumulation in the liver (IHL) is more strongly associated than VAT with:

- Insulin resistance and type II diabetes, Increased triglyceride levels, 2-3x higher coronary disease risk

Underlying mechanism not fully understood

How to measure?

- Adiposity and Liver Fat do not correlate
- Liver biopsy
- Blood test of γGT


Fabbrini, Intrahepatic fat, not visceral fat, is linked with metabolic complications of obesity, PNAS September 8, 2009 vol. 106 no. 36 15430-15435

Chitturi S. Fatty liver now, diabetes and heart attack later? The liver as a barometer of metabolic health. Journal of Gastroenterology and Hepatology. Vol 22, Iss 7, 967-969
MRI of Water and Fat

No Applied Field

Applied Field

measured signal
MRI provides the only *non-ionizing, non-invasive* method of assessing fat in its various compartments (subcutaneous-SAT, visceral-VAT, pericardial) and tissue fat content (liver-IHL, muscle-IMAT).

Quantitative regional measures of body fat may be more sensitive/specific for a range of metabolic diseases and for direct and indirect effects of therapeutics than simple measures such as weight / BMI.
MRI data on body fat imaging

Six adult healthy volunteers, M/F, 30-42 y/o.

‘Fat fraction’ images – intensity reflects fat content

- Large qualitative variability of visceral fat content in spite of similar outward appearance and average ‘build’ of all the volunteers.
- Subcutaneous fat correlates with BMI
- Visceral fat has poor correlation with BMI

Biogen
Biomarker Study with Alli

Serial MR study of the effects of Alli over 3 months

• Monthly
  • Physical: Weight (BMI), Waist Circ, BP, HR
  • Blood: Triglycerides, LDL/HDL Cholesterol
  • AEs: Alli known to cause GI upset
• Baseline and after 3 months of treatment with Alli
  • Multiple MR measures of fat compartment content at each timepoint
Bioamrker Study with Alli

3D Spatially resolved fat/water in torso

- Whole abdomen in 3 or 4 15s breath-held scans
- Total abdominal fat, visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), pericardial fat volumes (L)
Biomarker Study with Alli

MR Spectroscopy in (normally) low-fat regions

- Liver (Intrahepatocellular lipids - IHL)
- Muscle (Soleus and Tibialis Anterior)
  - Fat inside muscle cells-intramyocellular lipids (IMCL)
  - Fat in adipocytes scattered between muscle cells-extramyocellular lipids (EMCL)

Fat/water ratio 0.054

EMCL – CH$_2$
IMCL – CH$_3$

Cre
Water
Fat

Tau/IMA

Biogen
Results

24 out of 27 subjects completed, BMI = 27-35
Avg subject lost 5.24 Kg (5.6% mass, p<0.0001)
Avg BMI down by 1.72 pts (p<0.0001)
Avg Waist Circ. Down 4.54cm (4.3%, p<0.0001)
## Results – MR Endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>n</th>
<th>% Change</th>
<th>95% CI</th>
<th>Corresponding Absolute Change</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visceral Adipose Tissue (L)</td>
<td>20</td>
<td>-10.6</td>
<td>(-18.6, -1.8)</td>
<td>-0.60</td>
<td>(-1.05, -0.10)</td>
<td>0.0225</td>
</tr>
<tr>
<td>Subcutaneous Adipose Tissue (L)</td>
<td>19</td>
<td>-11.7</td>
<td>(-15.4, -7.8)</td>
<td>-1.01</td>
<td>(-1.33, -0.68)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total Abdominal Fat (L)</td>
<td>19</td>
<td>-12.2</td>
<td>(-16.9, -7.3)</td>
<td>-1.79</td>
<td>(-2.48, -1.07)</td>
<td>0.0001</td>
</tr>
<tr>
<td>IHL Fat-Water Ratio (%)</td>
<td>22</td>
<td>-43.3</td>
<td>(-56.7, -25.7)</td>
<td>-1.41</td>
<td>(-1.85, -0.84)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Pericardial Fat (L)</td>
<td>21</td>
<td>-9.8</td>
<td>(-17.9, -0.9)</td>
<td>-0.022</td>
<td>(-0.040, -0.002)</td>
<td>0.0342</td>
</tr>
</tbody>
</table>

Before Diet+Alli

3 mos Diet+Alli

Visceral: 5.330 to 3.961L : 25.68% fat loss
SubQ: 6.855 to 5.519L : 19.49% fat loss
## Results – Cardiovascular Sampling

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>n</th>
<th>Mean Change</th>
<th>95% CI</th>
<th>Corresponding Change</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>24</td>
<td>-0.546</td>
<td>(-0.780, -0.311)</td>
<td>-10.5</td>
<td>(-15.0, -6.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>High Density Lipids (mmol/L)</td>
<td>24</td>
<td>-0.063</td>
<td>(-0.112, -0.013)</td>
<td>-5.2</td>
<td>(-9.4, -1.0)</td>
<td>0.0168</td>
</tr>
<tr>
<td>Low Density Lipids (mmol/L)</td>
<td>24</td>
<td>-0.438</td>
<td>(-0.640, -0.235)</td>
<td>-13.4</td>
<td>(-19.7, -7.2)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>24</td>
<td>-0.087</td>
<td>(-0.262, 0.087)</td>
<td>-5.4</td>
<td>(-16.2, 5.4)</td>
<td>0.3074</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mmHg)</td>
<td>24</td>
<td>-6.04</td>
<td>(-10.33, -1.75)</td>
<td>-6.8</td>
<td>(-13.8, 0.2)</td>
<td>0.0027</td>
</tr>
<tr>
<td>Diastolic Blood Pressure (mmHg/L)</td>
<td>24</td>
<td>-4.92</td>
<td>(-7.25, -2.59)</td>
<td>-6.3</td>
<td>(-9.3, -3.3)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Heart Rate (beats/min)</td>
<td>24</td>
<td>-5.46</td>
<td>(-8.78, -2.14)</td>
<td>-8.6</td>
<td>(-13.8, -3.3)</td>
<td>0.0027</td>
</tr>
</tbody>
</table>

**IMCL/Cre** = 7.61 **Before Diet+Alli**  
**IMCL/Cre** = 6.29 **3 mos Diet+Alli**
Significant reductions from baseline to 3 month visit seen in Weight, BMI and waist circumference

- Waist Measurement associated with SAT, not VAT/IHL

Significant reductions in nearly all MRI endpoints

- Comparable reductions in SAT and VAT ~11%
- Strong correlations with weight loss
- No change seen in IMAT

Significant and largest reduction in IHL (-43%, p=0.0003)

Changes in IHL significantly associated with changes in blood pressure, heart rate and cholesterol

Changes in VAT only associated with weight and HDL cholesterol

Results also available including only those with BMI >= 28, near-identical values/changes.
Moving toward a pathology based classification of neurological disease
London, 1665:
Classification of disease

Shown by Sir John Bell
At PMWC2015 Oxford
Fast forward ~350 years...

Where is clinical neurology now?
We are pioneering a pathology targeting approach using biomarkers

**Diagnosis driven by constellation of clinical signs and symptoms**

Dementia | Movement Disorder | Weakness and Atrophy
---|---|---

**Molecular pathology and CSF analytes classify neurodegenerative diseases**

- AD (Alzheimer's disease)
- PD-dementia (Parkinson's Disease)
- PSP (Progressive supranuclear palsy)
- PD (Parkinson's disease)
- MSA ( multisystem atrophy)
- DLB (Dementia with Lewy bodies)
- FTLD (Frontotemporal dementia)
- ALS (Amyotrophic lateral sclerosis)

- β-amyloid
- tau
- α-Synuclein
- TDP-43
- SOD1

**Molecular imaging can visualize molecular pathology**

- β-amyloid
- tau
- α-Synuclein
- TDP-43
- SOD1

Under construction

AD Alzheimer’s disease; PD Parkinson’s disease; PSP Progressive supranuclear palsy; MSA multisystem atrophy; DLB Dementia with Lewy bodies; FTLD Frontotemporal dementia; ALS Amyotrophic lateral sclerosis.
A PRIME example: It’s all about the pathology

<table>
<thead>
<tr>
<th>Amyloid PET Negative %</th>
<th>ε4 non-carrier</th>
<th>ε4 carrier</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRIME(^1) (prodromal – mild; mean MMSE ~25)</td>
<td>57%</td>
<td>20%</td>
<td>39%</td>
</tr>
</tbody>
</table>

\[^{1}\text{Sevigny et al. (2016) Nature 2016}\]

[\(^{18}\)F]Florbetapir (Amyvid\(^{TM}\)) positron emission tomography (PET) at baseline and following 54 weeks aducanumab treatment.
Implementation of Amyloid PET Imaging In Aducanumab PRIME Clinical Trial

Amyloid PET approved by FDA for diagnosis of the presence of amyloid pathology and is used to enroll patients in clinical trials

- Evidence of target engagement and of dose- and time-dependent reduction in plaque load in the aducanumab treated patients


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Haeberlein et al, CTAD 2017
Thank you!