Leveraging Biomarkers in Early Clinical Drug Development for Metabolic Disease Therapies

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August 31, 2011
Overview of Presentation

- What is driving the need for innovation in early clinical research?
- Are biomarkers new?
- Why include biomarkers in early drug development?
- What are some examples?
  - Type 2 Diabetes
  - Lysosomal Storage Diseases
- What are the challenges?
  - Novel Biomarkers
  - Analytical Issues
  - Complex Study Logistics
- Summary
Clinical Development is Evolving

Traditional Paradigm: Phased Approach
- Pre-Clinical
- Phase I
- Phase II
- Phase IIb
- Phase III
- Test each scarce molecule thoroughly
- Scarcity of molecules from discovery

Emerging Paradigm: POC / Conformation Approach
- Pre-Clinical
- Proof-of-Concept
- Confirmation
- Shift attrition earlier
- Abundance of molecules from discovery

Importance of Proof-of-Concept Studies

*Defines Product Value For the First Time*

<table>
<thead>
<tr>
<th>Stage</th>
<th>% Chance of Reaching Market</th>
<th>Typical Costs ($million)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preclinical</td>
<td>0.1-1</td>
<td>IND tox study: 0.5 – 1.0</td>
</tr>
<tr>
<td>FIH study</td>
<td>5-10</td>
<td>FIH study: 0.7 – 1.4</td>
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<tr>
<td>POC study</td>
<td>10-30</td>
<td>POC study: 2 - 20</td>
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</table>
The Pressure is On for Proof-of-Concept!

- Increase in novel new drugs from discovery research
- More difficult disease states to study and treat
- Greater regulatory expectations on clinical trials
- Need for more informed decisions at clinical proof-of-concept
- Increased cost of clinical research
- Regulatory acceptance of adaptive-like study designs
- Expanding universe of new technology applications

Innovation
What is a Better Decision?

- One made earlier
- With greater confidence
- More efficiently

Better data, faster, cheaper
Q: Are Biomarkers New?
A. Biomarkers Are Not New.

Sushruta (clinician in India, 600 B.C.)
Recorded that urine of diabetic patients attracted ants

= Diagnostic biomarker for diabetes
Other Early Milestones in Biomarker Development

- **1555**  Józef Struś first measured blood pressure (by placing increasing weights on the skin over an artery until the pulse no longer lifted the weight)

- **1895**  Wilhelm Röntgen discovered x-rays → imaging biomarkers

- **1896**  Henri Becquerel discovered radioactivity → radiodiagnostics

- **1901**  Willem Einthoven invented the first ECG apparatus
An Early ECG Device

Photograph of a complete electrocardiograph, showing the manner in which the electrodes are attached to the patient, in this case the hands and one foot being immersed in jars of salt solution.
The Hybrid Phase I/ECG Core Laboratory

- Phase I focus only
- Single vendor with unified functionality
- Single database
- Single PM, DM, stats

**BLUETOOTH HOLTER**

- Instant ECG review
- Computer generated date/time stamp
- Preconfigured demographics

**HIGHLY AUTOMATED ECG PROCESSING**

- Single device to acquire safety ECGs during Holter recording
- 1000 sample/second acquisition
- Up to 48 hours ECG collection

- Automated, optimized ECG extractions from Holter
- Normal ECGs measured automatically providing lower variability—better data
- Cardiologist only review approximately 10-20%
- Faster data turnaround
Modern Era of Biomarkers – New Technology Drives Innovation

1950s to present day

Analytical Chemistry
- RIA/EIA/ECLIA
- GC
- HPLC
- LC-MS

“Omics”
- Genomics
- Proteomics
- Metabonomics
- Imaging
- Systems Biology
- Nanotechnology

Information Technology
Data Capture/Data Management

Biomarkers and Decision-Making

- Key question: How will the biomarker(s) advance the drug’s development?

- Primary purpose of biomarkers is to enable better decisions
Diabetes

- Diabetes affects nearly 25.8 million people (8.3% of the population) in the U.S.
  - 18.8 million diagnosed
  - 7.0 undiagnosed
- > 35% of U.S. adults > 20 years have pre-diabetes
- > 50 of U.S. adults > 65 years have pre-diabetes
- Leading cause of kidney failure, nontraumatic limb amputations and new cases of blindness
- Major cause of heart disease and stroke
- 7th leading cause of death
Plethora of Biomarkers for Diabetes

- Glucose
- Fatty Acids
- C-Peptide
- TGs
- Glucagon
- Insulin
- HbA1c
- Adiponectin
- TCF7L2
- PPARγ (glitazones)
- KCNJ11
- Gastric Emptying
- CRP
- TNF-α
- IL-6
- IGF
- IGFBP
- GIP
- GLP-1
- OCT1 (metformin)
- OCT2 (metformin)
- DPP4
- TNF-α
- IL-6
- OCT1 (metformin)
Considerations in Evaluating a Candidate Biomarker

- **Clinical relevance**
  - Ideally, should be related to MoA of the drug and the clinical endpoint

- **Sensitivity and specificity to treatment effects**
  - Ability to detect the biomarker or change in biomarker in the target population

- **Reliability**
  - Ability to measure the biomarker analytically with accuracy, precision, robustness and reproducibility

- **Practicality**
  - Is the biomarker non-invasive? Is it suitable to implement in multi-site trials?

- **Simplicity**
  - Simpler is better for translating a biomarker from lab bench to bedside
# SAD Study of a Novel DPP-4 Inhibitor in Mild Diabetic Patients

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<tr>
<th>Sequence</th>
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<th>Treatment Periods</th>
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<td>1</td>
<td>N = 5</td>
<td>P1: PLA</td>
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<tr>
<td></td>
<td></td>
<td>P2: 75 mg</td>
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<tr>
<td>2</td>
<td>N = 5</td>
<td>P3: 200 mg</td>
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<tr>
<td>3</td>
<td>N = 5</td>
<td>PLA</td>
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<tr>
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<td>P2: 100 mg</td>
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<td>N = 5</td>
<td>P3: 300 mg</td>
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<td>6</td>
<td>N = 5</td>
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Results of SAD Study in Mild Diabetic Patients: 
Early Evidence of Efficacy

Drug Plasma Concentration

Percent DPP-IV Inhibition

GLP-1 Concentration

Glucose Concentration

F=4-8%

Good Activity

Lower limit of quantitation

Lower limit of quantitation
SAD Study of Novel DPP-4 Inhibitor in Healthy Volunteers

High Inter-subject Variability in Postprandial GLP-1
GLP-1 Response to Meal is Different Between Healthy Volunteers and Type 2 Diabetics

Modest but Significant Decrease in Meal-Stimulated Intact GLP-1 in Type 2 Diabetes

*P < .05 for difference between type 2 patients with diabetes and healthy subjects.

Lysosomal Storage Diseases

- Rare inherited metabolic disorders that result from defects in lysosomal function

- Usually caused by the deficiency of a single enzyme involved in the metabolism of a lipid, glycoprotein or mucopolysaccharide, resulting in the excess accumulation of its substrate in the lysosomes

- Examples – Fabry disease, Gaucher disease, Pompe disease
Fabry Disease

- X-Linked inborn error of metabolism
- Subnormal or absent activity of lysosomal hydrolase, \( \alpha \)-galactosidase A (\( \alpha \)Gal A)
- Progressive globotriaosylceramide (GL-3) accumulation in tissues leading to end-organ impairment
- Most morbidity and mortality attributable to renal, neurologic and cardiac disease
- Therapies for Fabry Disease
  - Enzyme Replacement Therapy
  - Chaperone Therapy?
In Vitro Studies During Discovery Demonstrated $\alpha$Gal A as a Mechanism of Action Biomarker

Enhancement of $\alpha$Gal A in lymphoblasts from patients with Fabry disease

PD Biomarker Incorporated into Phase I Clinical Development Program

**WBC aGal A Activity in Healthy Volunteers During Treatment with AT1001 (150 mg bid)**

![Graph showing WBC aGal A Activity](image)
Gaucher Disease

- Most common lysosomal storage disease
- Autosomal recessive inheritance
- Subnormal or absent activity of lysosomal acid $\beta$-glucocerebrosidase (GCase)
- Progressive accumulation of substrate glucocerebroside in tissues leading to end-organ impairment
- Most morbidity and mortality attributable to hepatosplenomegaly, bone and neurologic disease

Therapies for Gaucher Disease
- Enzyme Replacement Therapy
- Miglustat (enzyme inhibitor that decreases production of substrate)
- Chaperone Therapy?
GCase as PD Biomarker in Phase I MAD Study

GCase activity in white blood cells during repeated daily oral doses of AT2101 for 7 days followed by a 14-day wash-out period.

DJ Palling et al., Am. College Med Genetics, Nashville, Tennessee, March 2007 (poster presentation)
Clinical Relevance of Biomarkers:

- If a biomarker is to be used to differentiate between healthy individuals and those with a disease, need to determine a priori the descriptive statistical parameters for the two populations
  - Mean, range, variance
  - Is there population overlap?
  - How does the population difference compare to the measurement error?

- May need to first conduct a survey study to collect data

- Determine appropriate sample size (based on statistical power to detect meaningful difference)
Example: Novel drug for treatment of a rare metabolic disease caused by an enzyme deficiency

- Phase II study: Patients were “pretreated” for 2 weeks with the drug to determine if they were “responders”. Only responders were to be enrolled in a 12-week open-label trial
  - Original definition of responder was “If baseline enzyme activity is less than 1% of normal, then Day -15 enzyme activity must be at least 2% of normal”

Key Issue: Need to define “normal”

- Measured enzyme activity in healthy subjects (N=21)
  - AVG = 22.8 nmol/mg protein
  - SD = 5.7, Range = 11.0 - 33.5
    - Cannot discern an increase from 1% to 2% of normal
    - Changed inclusion criteria based on X-fold increase from baseline for individual patient
Complex Sample Collection and Processing

Example – Phase IIa study – 14 tests, 7 labs

- Lab D
  Pharmacogenomic assay

- Lab B
  Clinical chemistry

- Lab G
  Future proteomics

- Lab C
  LC-MS/MS assay pathophysiological substrate and product

- Serum
- WBCs
- Non-coagulated blood

- Lab E
  Target enzyme assays

- Lab F
  Stimulated cell assay

- Heparinized blood
  Plasma
  freeze

- Lab A
  LC-MS/MS assay parent drug and metabolites
  freeze

- Urine
  Lab B
  Urinanalysis
  Add stabilizer

- Tissue Biopsy
  Add stabilizer
Challenges and Learnings

- Time to develop assay (translate from lab bench to clinic)
  - Assay through-put, sensitivity & specificity, reliability

- Defining normal baselines for novel assays
  - Can be readily done in early phase

- Complex sample collection and processing
  - Role of project management
  - Staff training (mock runs)
  - Barcode system to reduce errors, maintain chain of custody
Challenges and Learnings (…continued)

- High demands on data management and data analysis; quantity and speed
  - Integrated IT solutions

- Ethical issues (e.g. tissue banking, privacy, data integrity)
  - Issues must be recognized early and solutions developed early

- Evolving regulatory environment
  - Engage early with regulatory agencies
Summary

- Purpose of biomarkers is to enable better decisions
- Question to be answered should drive the technology used
- Understand biomarker variability and clinical relevance in study populations
- Recognize challenges and plan early