Using Biomarkers to Increase the Efficiency of Early Stage Drug Development

Personal consulting compensation received from Cytokinetics, Biogen, MT Pharma, Lilly, Karyopharm, Denali
Goals of Talk

- Describe definitions of types of biomarkers
- Show examples of useful biomarkers
- Biomarker development can accelerate and aid therapy development
What is a Biomarker?

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

Following the Science – why use biomarkers

Before introducing a drug into humans, we need to know:

1. Identity of the molecular target
2. Does the drug reach its target when administered to an intact organism
3. Once it reaches its target, can a pharmacodynamic effect be appreciated?
4. Does the safe and tolerated dose range for the drug include exposures that are likely to be efficacious based on #s 1-3?
5. Is the pharmacodynamic effect likely to generate clinical benefit?
## Six Main Categories of Biomarkers

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<thead>
<tr>
<th>Biomarker Category</th>
<th>Utility</th>
<th>Examples</th>
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| **Target Engagement** | • The drug interacts with its intended molecular target *in vivo* | • PET receptor occupancy studies  
• Measurement of molecular complexes *in vivo*  
• Binding in a surrogate compartment (e.g., lymphocytes) |
| **Pharmacokinetic** | • The drug reaches its desired molecular site of action | • Pharmacokinetics in CSF  
• CNS uptake studies |
| **Pharmacodynamic** | • The intended molecular effect produces the desired biological effect.  
• Useful for determining therapeutic dose range;  
• potential candidate for becoming a surrogate | • Effect on Molecular Target:  
• Effect on Presumed Downstream Marker  
• Plasma proteomics  
• Plasma metabolomics |
| **Diagnosis/Stratification** | • The targeted disease state is present, and/or the desired patient population can be stratified to optimize risk benefit ratio and probability of success | • Genetics  
• Blood-based makers  
• CSF  
• Imaging |
| **Disease Outcome** | • Assessment of effect on Clinical or Pathological Disease measures | • Clinical Outcome Measures  
• Imaging  
• Anatomical  
• Functional |
| **Safety** | • Presence and/or severity of potential target organ toxicity is measurable | • Biochemical (common/special labs)  
Electrophysiological (QTc) |
Integration of Biomarker Strategies into Drug Development Decision Making

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<thead>
<tr>
<th>Decision Points</th>
<th>PDCR</th>
<th>FIH</th>
<th>Ph.2</th>
<th>Ph.3</th>
<th>Filing</th>
<th>Launch</th>
<th>LCM</th>
<th>Post-launch</th>
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Courtesy of Jesse Cedarbaum
Ceftriaxone in ALS: Three STAGE Adaptive Design

STAGES 1 and 2

66 Subjects

- 21 Subjects (0g)
- 23 Subjects (Ceftriaxone 2g)
- 22 Subjects (Ceftriaxone 4g)

STAGE 3

447 Subjects

- 151 Subjects (Placebo)
- 296 Subjects (Ceftriaxone 4g)

Total 513 Subjects

- Total 172 Subjects (Placebo)
- Total 341 Subjects (Ceftriaxone 4g)
STAGE 1 Pharmacokinetics

**Plasma Ceftriaxone (µg/mL)**

- **HOURS**
  - 0
  - 2
  - 4
  - 6
  - 8
  - 10
  - 12

- **PLASMA CEFTRIAXONE (µg/mL)**
  - 20
  - 50
  - 100
  - 200
  - 300

**Pre-Dose Plasma Ceftriaxone (µg/mL)**

- **WEEK 1 VALUE**
  - 20
  - 40
  - 60
  - 80
  - 100
  - 120
  - 140

- **WEEK 4 VALUE**
  - 20
  - 40
  - 60
  - 80
  - 100
  - 120
  - 140

**Dosages**

- **2 gm/day**
- **4 gm/day**
STAGE 1/2: Both Dosages Achieved Trough CSF Cut off Goal of 1 uM; Both dosages Tolerable

All Dosages Tolerable – complete 20 weeks

Placebo 76.2% (16/21)
2 grams 87% (20/23)
4 grams 78.3% (17/22)

Ceftriaxone pharmacokinetics in ALS similar to other populations; plasma levels predict CSF levels
**P_D** Markers: measure of compounds ability to interact with its intended target leading to a biological effect.

- **P_D type:**
  - Biochemical:
    - Enzyme substrate
    - mRNA/ Protein
  - Imaging:
    - PET
    - MRI
    - CT

- **P_D use:**
  - Test biological hypothesis in human
  - Combine with **P_K**
  - Select dose:
    - Efficacious range
    - Safe range

**Disease models:**
- In vitro
- In vivo

**Micro-imaging:**
- PET
- MRI
- CT

Courtesy of Gilmore O’Neil
SOD1 in the CSF as a PD Biomarker for ALS

- SOD1 Antisense Oligonucleotides (ASO) lower SOD1 and prolong survival in animal models
- SOD1 natural history data suggests we will be able to determine benefit
- ASOs safe in prior IONIS Phase I in SOD1 ALS

52 participants;
50% extension survival
80% power

Tim Miller, Washington University
Antisense Oligos Decrease SOD1 in CSF in SOD1 G93A Rats

- **Brain SOD1 Protein**
- **CSF SOD1 Protein**

![Graph showing the decrease in SOD1 protein levels in CSF and brain with antisense oligos compared to saline control. The R² value is 0.93766.](image-url)
SOD1 in CSF Varies Little Over Time

Winer et al. 2013, JAMA Neurology

Average 7%

Bob Bowser
David Lacomis
BIIB067 Phase I SAD/MAD Study Design

ALS Patients

Cohort 1
14 days +Safety Review

Cohort 2
14 days +Safety Review

Cohort 3
14 days +Safety Review

Cohort 4
14 days +Safety Review

Part A
Single Ascending Dose

SOD1 ALS Patients

Cohort 5
106 days +Safety Review

Cohort 6
106 days +Safety Review +SOD1 PD Review

Cohort 7

Targeting CSF SOD reduction

Objectives

1: Safety and tolerability
2: CSF SOD Reduction
Ex: Effect of BIIB067 on measures of electrophysiology, strength, clinical function
[\textsuperscript{11}C]PBR-28 identifies activated microglia in ALS

Increased binding to activated microglia in Motor cortex and other areas of interest for ALS.

Potential use as PD marker in trials that target microglial activation (RNS60, ibudilast)

Diagnosis/Stratification biomarkers can help define population most likely to respond to a treatment.

Retigabine trial in ALS only in people with documented motor neuron hyper-excitability.
NP001– CRP example

- CRP was first reported by Tillett and Francis in 1930 and was named so because it was discovered as a substance in the serum of patients with acute inflammation that reacted with the C-(capsular) polysaccharide of Pneumococcus. J Exp Med. 1930;52(4):561–71.

NP001-Responder analysis: how many participants did not change in ALSFRS-R

From Miller et al., 2015
Change in ALSFRS-R in Patients with high c-reactive protein

Patients with CRP greater than median level

Courtesy Robert Miller
New study of NP001 completed enrollment

- Preselected participants for the presence of inflammation as measured by c-reactive protein.
- Double blind, placebo controlled trial
- Primary outcome measure is change in ALSFRS-r
- 120+ participants, 6 month treatment
The NeuroNEXT Network: Early development trials, biomarker focus

www.neuronext.org
NeuroNEXT NN101 Study: Spinal Muscular Atrophy (SMA) Biomarkers in the Immediate Postnatal Period of Development
Study Design

• Prospective, longitudinal cohort study to identify biomarkers of disease progression in SMA

• Participants enrolled between 0 and 6 months from birth and followed until two years of age (normal controls healthy children and those with SMA)

• Participants underwent a number of assessments including SMA genotyping, motor function assessments, clinical exams, CMAP and blood draws
Study Endpoints

- Motor Function Scales
  - Test for Infant Motor Performance Screening Items (TIMPSI)
  - Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND)
  - Alberta Infant Motor Scale (AIMS)
Study Endpoints

- Putative Physiological Biomarkers
  - Electrical Impedance Myography
  - Compound Motor Action Potential (CMAP)
  - Weight

- Putative Molecular Biomarkers
  - SMN mRNA Levels
  - SMN Protein Levels
  - SMAF SMA Signature Panel
Primary Objectives

**Primary Objective 1:**
Describe and compare the distribution of motor function assessments over the first two years of life in SMA vs. healthy control infants.

**Primary Objective 2:**
Describe and compare the distribution of putative physiological and molecular biomarkers over the first two years of life in SMA vs. healthy control infants.
Secondary and Primary Progressive Ibudilast NeuroNEXT Trial in Multiple Sclerosis

- 96-week, 250-subject, randomized, placebo-controlled phase II trial of ibudilast (PDE- and MIF-inhibitor) in SPMS/PPMS
  - Concurrent treatment with IFN-β1 or GA is allowed
- Primary Outcome: whole brain atrophy (BPF)
  - Secondary Outcomes:
    - DTI (descending pyramidal tracts)
    - MTR (whole brain)
    - OCT (retinal nerve fiber layer)
    - Cortical atrophy (CLADA)
- Utilizing NeuroNEXT, a US-based, NIH-funded Phase II clinical trial network
- Head-to-head comparison of imaging measures
  - Longitudinal validation to clinical outcomes
Biomarker development can accelerate and aid therapy development

Useful throughout development of treatment
- Target Engagement
- PK/PD biological activity
- Diagnosis/Stratification
- Disease Outcome
- Safety/Toxicity

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