Biomarker Development for TBI

Chair: Gary Small, MD, Semel Institute for Neuroscience & Human Behavior, David Geffen School of Medicine at UCLA

Members:
Ronald Hayes, PhD, Banyan Biomarkers, Inc
Patrick M. Kochanek, MD, MCCM, Department of Critical Care Medicine, University of Pittsburgh School of Medicine
Andreas Jeromin, PhD, Quanterix, Inc
Steve Potkin, MD, Department of Psychiatry, UC Irvine
Ira Shoulson, MD, Department of Neurology, Pharmacology and Human Science, Georgetown University
Douglas Smith, MD, Department of Neurosurgery, Perelman School of Medicine, University of Pennsylvania
Overview

• Biomarkers
  – Objectively measured characteristics indicating normal biological or pathogenic processes, or pharmacologic responses to a therapeutic intervention

• Clinical endpoints
  – Variables that reflect or characterize how a study subject in a clinical trial “feels, functions, or survives”

• Surrogate endpoints
  – Biomarkers that can be trusted to serve as stand-ins for clinical endpoints
  – Require solid scientific evidence (e.g., epidemiological, therapeutic, pathophysiologial) that a biomarker consistently and accurately predicts a clinical outcome

Benefits of Biomarkers as Surrogate Endpoints

• Increase diagnostic accuracy/homogeneity of subjects in clinical trials for stratification and enrichment
• More accurate dosing and monitoring of treatments
• Provide researchers interim/early evidence about safety/efficacy of treatments
  – Reduce risk of harm to subjects
  – Allow researchers the opportunity to stop potentially ineffective or harmful interventions
  – Circumvent primary clinical endpoints, which may occur infrequently making their use in clinical trials impractical, or even unethical
• Shorten time to approval of new treatments, allowing effective treatments to reach target patient populations sooner
Challenges to TBI Biomarker Development

• Variability in type, timing, and duration of injury
  – Acute vs. chronic, civilian vs. military

• Pathophysiological complexity of short-term and long-term injury
  – Multiple interrelated disease pathways may be involved
  – Biomarkers might be indirect signs of pathways that are not fundamental to the key disease processes
  – Variable blood brain barrier injury and the complex contribution of efflux via the glymphatic system represent special challenges to successful development of serum biomarkers of brain injury

• Even biomarkers statistically validated as surrogates for a given clinical endpoint may not actually be part of the pathophysiological pathway that results in that endpoint

• Need for proactive involvement and guidance from stakeholders, including FDA, federal funding agencies, and TBI biotechnology and scientific communities
Biomarker & Clinical Endpoint Example 1

- Disease: Mild, Severe
- Biomarker 1
- Clinical features
- New treatment started
Biomarker & Clinical Endpoint Example 2

Disease

Mild

Severe

Baseline

Time

New treatment started

Clinical features

Biomarker 2
Biomarker May Signal Need for Early Treatment that Improves Outcome

- Clinical features
- Biomarker
- Standard treatment

Graph showing disease progression over time with early treatment indicating improvement compared to standard treatment.
Why Treatment/Biomarker Development Fails

- Overemphasis on singular disease mechanisms
  - e.g., amyloid in Alzheimer’s drug development
- Treatment trials too late or too early in disease progression
- Individuals/research groups championing only their target(s) of interest
- Over-reliance on “consensus science”
  - Science requires only one investigator who produces verifiable and reproducible results
  - “…it is the consensus in the field” – used as a justification for shutting down ideas not associated with beliefs
- Lack of clarity/education on translational pathways from bench to bedside to curbside
- Inefficient “interfacing” between academia and industry

How Biomarkers Might Facilitate TBI Therapy Development

- Objectively quantify injury severity
- Predict patient outcome/risk for later neurodegeneration
- Identify injury mechanisms/therapeutic targets
- Assess time course of pathobiological responses to TBI and therapeutic windows
- Aid in assessment of therapeutic efficacy
- Monitor recovery of function or decline rate
- Aid in assessment of CNS drug toxicity
Examples of Potential Resources

• Operation Brain Trauma Therapy (OBTT)
  – Multicenter preclinical drug-screening consortium that screens TBI therapies

• TBI Endpoints Development (TED)
  – Establish multicenter team to ID-validate assessments/outcomes/biomarkers

• Post-hoc Analyses of Data from Ongoing/Previous Research
  – Biomarkers of Injury and Outcome in ProTECT III (BIO-ProTECT III): collected during failed progesterone trial
  – ALERT-TBI (Banyan Biomarkers, Inc): multicenter pivotal trial seeking to validate clinical utility of UCH-L1 and GFAP for acute TBI diagnosis
  – TRACK-TBI Multicenter Initiative – test/refine biomarkers in TBI
  – ADNI DoD – examines connections between TBI and PTSD

• Biomarkers Developed for Other Disease Processes
  – Alzheimer’s, inflammation (multiple sclerosis), Parkinson’s
Future Pathways

- Create and ensure funding for large multi-site/inter-disciplinary teams (e.g., ADNI [Alzheimer’s Disease Neuroimaging Initiative])
- Diversify research pathways and target portfolios
- Determine priority disease states/stages for treatment/biomarker development
- Expand available funding for individual projects (e.g., R01s) to foster new ideas/strategies
- Base funding and strategic planning on broad and dispassionate interpretation of the evidence rather than belief systems and research areas of personal interest
- Foster team-work among diverse disciplines
- Initiate trials using biomarkers developed in related areas (e.g., Alzheimer’s/stroke)
- Engage relevant stakeholders and provide incentives for collaboration
Immediate Action Items

• Identify champion(s) vested with the authority and resources to create an effective partnership with the FDA, which would name specific participants within the FDA and their roles and responsibilities

• The mission of this partnership would be to articulate FDA sanctioned pathways to use biomarkers to accelerate TBI drug development, clinical trial design and assessment of neurotoxicity

• FDA guidance would include defining different regulatory steps for different biomarker applications (e.g., diagnostic vs. surrogate markers)

• Once a framework for these pathways has been established, a broader discussion with stakeholders can take place, including the identification of needed resources and timelines