Biomarkers as Drug Development Tools

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Biomarkers
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The Value Proposition for Translational Safety Biomarkers as Tools for Drug Development

Frank D. Sistare
Merck and Co., Inc.
On behalf of the C-Path PSTC

November 30, 2011, Silver Spring, MD
• 43% concordance between clinical trial toxicities & rodent toxicity seen across 150 cmpds; 63% in nonrodents (71% in any one species)

• Clinical toxicity predictions vary by organ system as well as species dropping to as low as 36% (when seen in any one species)

How can we guard against such drug-induced injuries seen in the clinic but not in preclinical toxicology studies?

How can we advance development of good drugs showing toxicities in animals that are not expected to present in humans?
Non-Clinical Development – Problem Statement


- 2000: Phase 1 Costs - $31M. Phase 2 - $42M. Phase 3 - $129M.

- 2005: Cost per marketed drug - $500M Preclinical + $800M Clinical.

The longer we delay awareness of relevant clinical safety issues the greater the costs of development failure.

When we discard compounds with animal study toxicities that reflect irrelevant clinical safety issues, we delay success and escalate development costs.

Eliminating the need for repeating, or avoiding unwarranted progression of just one compound’s Phase 1 or 2 trials could save over $31–42 million in development expenses when specific safety concerns can be confidently addressed using new qualified TSBs.
Goal: Improve speed/efficiency to arrive at critical datasets and/or generate more robust preclinical risk assessment data to improve internal candidate selection decisions for clinical development.

- Optimize animal testing
- Improve human risk assessment
- Enhance clinical trial safety
- Increased efficiency and ↓ cycle time
- ↓ Animal use
- ↓ Development costs and delays

Need for Global Regulatory Alignment
Incorporating New Qualified Safety Biomarkers in Drug Development

- Novel Accessible Translational Safety Biomarkers

  - Enable continued clinical development of drugs suspected of human irrelevant animal toxicities—ensuring patient safety, reducing drug failures, and loss of time

  - Longitudinal monitoring in animal studies optimizes and minimizes animal use

- Example: New kidney safety biomarkers can outperform serum creatinine and BUN
  - FDA, EMA, PMDA Qualification

Nature Biotech. May 2010
10 manuscripts
Future progress of safety biomarker qualification will be stymied if it continues to grow more cumbersome and costly. There is a need for resolution in a globally coordinated manner.
Need for Qualified Translational Safety Biomarkers (TSBs)

Box 1. Examples of unmet needs in drug development for additional accessible translational safety biomarkers.

**Liver injury**
- Improved biomarkers are needed with:
  - Enhanced tissue specificity over ALT for liver injury;
  - More sensitive and earlier detection to inform liver dysfunction, injury response, molecular toxicology mode-of-action (and not just report membrane leakage);
  - Capability to inform patient prognosis and differentiate high-risk from low-risk occurrences of seemingly similar ALT elevations;
  - Translational biomarkers with sensitivity and specificity for biliary hyperplasia.

**Vascular injury**
- Biomarkers or imaging approaches are needed to inform acute vessel damage, including degeneration, inflammation and hemorrhage, and also to allay hypothetical concerns over atherosclerotic plaque progression, thrombus formation and destabilization.

**Neurotoxicity**
- Accessible translational safety biomarkers (TSBs), including imaging, of neuronal injury including CNS pathologies as well as peripheral neuropathies are needed.

**Pancreatitis**
- Early TSBs with improved sensitivity over amylase and lipase are needed.

**Tissue fibrosis**
- Accessible biomarkers or imaging approaches could address tissue specific safety concerns relating to chronic organ injury and fibrosis, as well as perhaps even monitor disease progression and response to intervention (e.g., liver fibrosis and hepatitis C).

**Bone & cartilage damage**
- Arthropathies may follow destruction of chondrocytes and joint cartilage; qualified biomarkers are needed to address treatment-related concerns regarding acceleration of osteoporosis and enhanced risk for bone fracture.

**Phospholipidosis**
- Phospholipidosis histomorphological changes may be seen in rodent toxicology studies, and often not in other species. Human relevance and toxicological significance remain questionable. A satisfactory monitorable biomarker strategy could enable drug development and dispel lingering concerns over long-term patient safety.

**Testicular injury**
- Such findings may limit early clinical trial designs to females, excluding males, until greater understanding of the effect is achieved, or until a back-up compound devoid of such findings is identified.

**Gastrointestinal**
- Accessible mucosal damage biomarkers, for example, that could specifically alert this safety concern may reduce the need for endoscopic examinations in clinical trials and assist with patient enrollment.

**Tumorigenesis**
- A diverse set of qualified biomarker panels that could be integrated in the course of drug development animal toxicology studies in order to elucidate mode-of-action for nongenotoxic compounds and enable human relevance assessments using specimens collected from both the animal studies as well as clinical trials.

*ALT: Alanine aminotransferase.*
Sponsor Considerations in Deciding to Contribute to Consortia Dedicated to Qualification of New TSBs

- Is the multiyear commitment sufficiently meritorious to compete resources away from corporate priorities & direct projects?
  - Can hurdles be reduced by health authorities to shorten the time commitments?
  - Can regulatory processes and decisions be harmonized globally?

- Does the collaboration leverage contribution equitably across consortia members or will one or two companies assist competitors more than the benefit received?

- Does the scope of the effort require data sharing with competitors, or is the objective one that would provide a competitive advantage and not require public disclosure of internal company investment?

- Are other consortia already engaged in the same effort or are they able to share strategy, data, samples, and coordinate activities so as to be complementary?

- Is the structure, management, leadership, sponsorship and program support of the consortium likely to generate success?
Vision: MRI as a Histopathology Surrogate in Assessing Target Organ Toxicity to Complement TSBs

Non-Invasive Biomarker of Organ Injury

+ Traditional and Novel Biomarkers

Assessments
- Volume
- Blood Flow/Perfusion
- Morphology
- Functional Activity
- Differential Tissue Contrast
- Metabolite Concentration by MRI/MRS

Examples
- Serum Biochemistry
- Hematology
- Urinalysis
- ECG
- Ophthalmology
- Novel Biomarkers
  - Urine KIM-1 etc.
  - New Innovations
    - e.g., micro RNAs

‘Real-Time’ Longitudinal Assessment

Reduce/eliminate the need for multiple NONRODENT studies & necropsies while maintaining assurances of clinical trial safety

Bridging Biomarker

Targeted Translation into clinical setting as needed

Brain

Thyroid

Kidney
Additional Qualified TSBs are Needed to Enable Drug Development by:

1. …enhancing the value of animal toxicology studies

2. …enhancing safety monitoring of patients in early clinical trials for toxicities seen in animal studies that are of questionable human relevance, and

3. …by reducing decision-making ambiguity in clinical trials with data that can provide greater diagnostic insight over conventional biomarkers alone, allowing improved patient prognosis and greater understanding of drug action.
Safety Biomarker Prioritization and Translation

Two sides of the same coin

Rich Miller
GSK
C-Path/PSTC Co-Director
Safety Biomarker Prioritization

Drivers

• Attrition data (preclinical/clinical)
  - Cardiovascular toxicity
  - Hepatotoxicity
  - Nephrotoxicity
  - Other target organs less frequently (e.g., testicular, ocular)

• Clinical perspectives and needs
  - Confidence in ability to detect specific organ effect with current cadre of safety biomarkers
  - Patient population versus preclinical species
  - Project specific

• Feasibility (technical, discovery/preclinical data)
Safety Signal

> Translation

- Translation of preclinical effect
  - Functional impact?
    - *normal animal or human versus patient(s)*
    - *how important is this functional disruption in people?*
  - Detectable with current modalities?
  - Species specific? Are you sure?
  - Severity of impact?
    - *is minimal impact of concern?*
  - Time to onset, shape of dose response curve
  - Adaptation
  - Target mediated?
  - Class effect?
  - Impact on clinical trial design/cost to monitor
  - Data from other studies (in vitro, efficacy, other in vivo safety studies, etc)
• Translation of preclinical effect (cont’d)

> Apples to apples
  - Toxicities are heterogenous and often evolve (e.g., for hepatotoxicity; cholestatic, mixed and hepatocellular)
  - Pathophysiology and functional sequela may be different across species
  - Step check on terminology (e.g., “transaminitis”, “LFTs”)

> Metabolic differences

> Reserve capacity
  - Impact on functional reserve

**Safety biomarkers are essential data but must be interpreted in an integrated manner in the broader context of all relevant data**
Safety Biomarker
A recurring scenario

BILIARY HYPERPLASIA
Biliary Hyperplasia

- No/minimal change in routine hepatic biomarkers
  - GGT slightly increased, no change in ALT, AST, bilirubin, or ALP
  - Not seen in non-rodent species at comparable exposures

- Concern? What does it mean?
  - low grade or localized cholestasis
  - direct/indirect mitogenesis
  - regenerative response after prior cholangiocyte or periportal hepatocyte injury
  - biliary vascular plexus disruption

- There is hope;
  - Routine hepatic transcriptomic assessments.
Other recurring liver scenarios

- Hepatocyte vacuolar degeneration/rarefaction

- Hepatic fibrosis

- Hepatic inflammation

> decreased miR-29?
Summary/Future

• The “coin” is the target organ and all the knowledge, data (including safety biomarkers), and prior experience that guide translation

• Preclinical models underpin fundamental pathophysiologic safety biomarker knowledge supporting clinical progression
  > challenges exist in clinical qualification of biomarkers

• There are clearly gaps in systems knowledge and tools, including amongst the currently used safety biomarkers but...

• These gaps are being filled through collaborative efforts of the PSTC with numerous exploratory safety biomarkers on the way for not only liver, but heart/vasculature, kidney and skeletal muscle

• Biomarker knowledge accrual is a life long endeavor

Creating Consensus Science: New Tools and Tactics for Next-Gen Drug Development

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FDA

CDISC
Opportunities

• Safety data sharing through PSTC can further elucidate predictivity of preclinical safety signals by combining member company translational data
Why biomarkers are essential to meet the challenge of developing drugs for neurological diseases.

Gary J Romano, Ph.D., M.D.
Neuroscience Biomarkers
Janssen R&D
Spring House, PA
MORE MEDICAL RESEARCH IS NEEDED TO DEFEAT ALZHEIMER'S DISEASE BEFORE IT'S TOO LATE TO HELP THE BABY BOOM GENERATION.

By Sandra Day O'Connor, Stanley Prusiner and Ken Dychtwald

“As things stand today, for each penny the National Institutes of Health spends on Alzheimer's research, we spend more than $3.50 on caring for people with the condition”

— Quotes from The New York Times

Traumatic Brain Injury & Depression may be associated with an increased risk of developing Alzheimer’s Disease

Report from the Lewin Group, commissioned by the Alzheimer’s Association, Washington DC, 2004
Serious Neuropsychiatric Disorders
Among the Most Disabling Illnesses, Associated with Tremendous Suffering

- Share of 2015 Burden of Disease (% of Total Disability Adjusted Life Years)

  Neuropsychiatric disorders
  Malignant neoplasms
  Cardiovascular diseases
  Injuries (including self-inflicted)
  Sense organ disorders
  Respiratory diseases
  Communicable diseases and...
  Musculoskeletal diseases
  Diabetes mellitus

European Brain Council Study Annual cost of brain disorders in Europe now 798 billion euros ($1 trillion)

WHO 2015 DALY baseline scenario for high income countries

WHO Statement: “...unless immediate action is taken globally, the neurological burden is expected to become an even more serious & unmanageable threat to public health”
The human brain is the most complex object of study in the history of science and one of the most inaccessible

- **Expertise** is scattered, approach to research is **fragmented**, and resulting datasets are **siloed**

- **Incentives** for research and collaboration are **lacking** and/or **misaligned**

- Declining federal and industrial support is leading to **diminished pipelines**
CNS disorders present difficult challenges for drug development...

**Challenges**

Uncertain target engagement
- Difficult to detect PD effects in CNS compartment

“Noisy readouts”
- Cognitive function, mood, psychosis, pain

Population heterogeneity
- Syndromic classification in neurology and psychiatry

Insidious onset and slow progression
- Larger and longer trials

**Pitfalls**

Errors in dose selection

Need large N to detect small signals

Diagnostic uncertainty, Low responder rates

Larger and longer trials

↑ Variability
↓ Treatment Effect Size

POOR SIGNAL DETECTION
Biomarkers that improve assessment of disease and drug effects:
Target Engagement, Pharmacodynamic, Efficacy, Disease Progression Markers

Improved signal detection

More Informed Decisions

Smaller and less expensive studies

More compounds tested in more indications

Patients benefit from novel therapeutics

Diagnostic Biomarkers that improve characterization of patients:
Predictive and Prognostic Markers

Enrichment, Patient Stratification

Patients benefit from Personalized Medicine

The effective use of biomarkers can increase the probability of success …
Biomarkers in Neuropsychiatric Disorders: heterogeneous, composite, and complex
Effective use of Biomarkers for Drug Registration will require Collaboration and Consensus

“Biomarker Qualification: within stated context of use, the results of assessment...can be relied upon to have a specific interpretation and application in drug development and regulatory decision-making. “

Advantages of Collaborative Approach:

• Data Sharing:
  • Large data sets not available from individual companies or trials
  • Standardization Across trials and sponsors
  • From different sources
  • From different targets and compounds

• Sharing of Best Analytic Practices
  • Advanced clinical informatics, computational biology, visualization tools

• Open dialogue
• Close interaction with Health Authorities
Accelerate the Drug Discovery Path to Advance Effective Treatments for Alzheimer’s and Parkinson’s Disease

➢ **Advance** drug development – “Tools”

- **Develop** common data standards
- **Create** public databases of pooled clinical trial data
- “Qualified” biomarkers (FDA Draft Guidance 2010)
- “Accepted for use” Quantitative disease models
Collaborative Effort to Facilitate AD drug development: Biomarker Qualification and Disease Model Acceptance

Quantitative Model of Alzheimer’s Disease Progression

$S(t) = S_0 + \alpha \cdot t + f_{obs}(t) + f_{mod}(t) + \varepsilon$

Hippocampal Volume Predicts Progression to AD

In AD and in cognitively impaired patients at risk of progressing to AD dementia, CSF Aβ42 is low and t-Tau and pTau181 is high.


“Basic biomedical science will churn out candidate biomarkers with tantalizing potential to improve value, whereas methods to use them effectively in drug development will evolve more slowly. The balance between these forces may well determine the success or failure of the drug development enterprise over the next decade.”

- Janet Woodcock

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We share the problem -- and have to work together to find solutions
Autosomal Dominant Polycystic Kidney Disease

Limitations of current biomarkers and the need for new biomarkers

Ronald D. Perrone, M.D.

- Immediate Past Chairman, Scientific Advisory Committee, PKD Foundation
- Associate Chief, Division of Nephrology, Medical Director of Kidney Transplantation, Tufts Medical Center
- Professor of Medicine, Tufts University School of Medicine
Autosomal Dominant Polycystic Kidney Disease (ADPKD)

- Hereditary systemic disorder characterized by bilateral kidney cysts
- Progressive renal insufficiency leading to kidney failure in ~50% of patients
- Extrarenal manifestations + all CKD related issues
- Frequency: 1/500 to 1/1000
- ~600,000 in USA; 12.5 million worldwide
- Accounts for 8 to 10% of patients on dialysis
- Direct medical costs exceed $1.5 billion/year
- Substantial indirect costs including pain and suffering, unemployment, and family disruption due to multiple generations possibly requiring transplant or dialysis
22 Kg Total

Courtesy J. Grantham
Age of ESRD: How well are we doing?

Mean Age at ESRD Onset

USRDS, courtesy of Eric Weinhandl
The Dilemma

• Progression of ADPKD to renal failure takes on average 55 years.

• The manner of progression is such that kidney function (GFR or glomerular filtration rate) remains stable for many years, while enormous structural derangement of kidneys occurs.

• Earlier biomarkers of kidney progression are needed.
Opportunity for Intervention

• The ideal therapeutic agent would block formation and/or growth of cysts at an early stage of life, thereby preventing the *inexorable* expansion, irreversible scarring, and structural distortion of kidneys, which are associated with all of the kidney complications of ADPKD.

• Adoption of total kidney volume (TKV) as a target endpoint for regulatory approval will greatly accelerate the pace of clinical research and introduction of new therapies, thereby benefiting all PKD patients.
• Goal is to create disease progression models to generate scientific consensus on the utility and reliability of TKV as a biomarker and clinical endpoint for the progression of ADPKD.

• The disease models will be used as evidence in a formal application to the FDA and the EMA for qualification of TKV as a biomarker for a specific context of use in ADPKD clinical trials.
History

• Multiple meetings with FDA, beginning 5/17/07

• Recommendation from FDA to construct disease model to ascertain linkage between TKV and rate of size increase and common secondary features of ADPKD:
  – hypertension, hematuria, pain, abdominal fullness, renal stone, renal infection, creatinine clearance

• Recognition that data residing in existing registries and being collected in ongoing clinical trials is not in a standardized format

• Collaboration with CDISC and C-Path to standardize data
PKD Database

• Established CDISC data standards
• Remapping and pooling data from 3 patient registries, 2 NIH clinical trials and additional trials for >2600 patients
• Database open to Consortium researchers
  • Once complete, will be open to qualified researchers globally
Disease Progression Model to support qualification of TKV

1. Biomarker-Disease Model

TKV Expansion → Disease Outcomes

Regulatory Qualification of TKV as Imaging Biomarker

Disease outcomes:
- End-Stage Renal Disease
- Mortality
- Worsening of Renal Function
- Time to Doubling of Serum Creatinine
- Achievement of CKD Stage 4
- 20% and 50% worsening of eGFR
- Hypertension
- Gross hematuria
- Kidney stones
- Urinary tract infections
- Ruptured intracranial aneurysms
- Hospitalization for complications of PKD

2. Drug-Biomarker Model

Dose → Systemic Exposure → Inhibition of TKV Expansion → Improved Disease Outcomes

3. Drug-Biomarker-Disease Model

• sources of variability
Changing the Paradigm

Desired future endpoint

Concentrating defect, Hypertension, Proteinuria

Present endpoint

Pain, Hematuria, Stones, Infections

Kidney function (%)

Age (years)
Value of Consortium Approach

• Collaboration
• Open dialogue
• Data sharing
• Diversity of skillsets and expertise
• Efficiency
• Resource sharing
• Close interaction with FDA
Questions for discussion

• What are the benefits of collaboration in the precompetitive space for biomarker qualification?
• What is the value of biomarker qualification? How can we measure the utilization and value of newly qualified biomarkers?
• What factors should be used to prioritize which biomarkers are submitted for qualification?
• What are the limitations of current biomarkers?
F. SISTARE BACKUPS
Inability to confidently monitor patients for toxicity

Delays in development timelines for patients with significant medical needs due to inappropriate loss of drug candidates

Problem:
Histopathological lesions often observed at doses and times where no measureable changes in sCr or BUN detected
Single species effect or human irrelevant mechanisms suspected

Proposed project deliverable: Regulatory qualification of a new set of biomarkers that outperform sCr and BUN for monitoring early onset and reversal of mild kidney injuries
Following assessment, both regulatory agencies came to the conclusions that:

- the renal biomarkers submitted were acceptable in the context of non-clinical drug development for detection of acute drug-induced renal toxicity;

- the renal biomarkers provide additional and complementary information to the currently available standards;

- the use of renal biomarkers in clinical trials is to be considered on a case-by-case basis in order to gather further data to qualify their usefulness in monitoring drug-induced renal toxicity in man.
Criteria adapted from Altar, et al, and Bradford-Hill for defining the strength of evidence to support the qualification of a new safety biomarker (agreed link to biology and clinical outcome)

- Availability of a sufficiently validated analytical assay
- Support for biological plausibility of a biomarker's association with organ injury
- Understanding of the molecular mechanism of the biomarker response
- Strength of association demonstrating linkage of the biomarker change to pathology outcome and improved performance relative to currently accepted biomarkers
- Consistency of response across mechanistically diverse and relevant organ toxicants; and across sexes, strains, and species
- Presence of both a dose-response and temporal relationship relating the magnitude of the biomarker response to severity of injury, and the onset and recovery of injury to correlative and timely changes in the biomarker
- Appropriate specificity of the biomarker to not respond to agents which injure other organs but do not injure the target organ, or which activate physiological processes within the target organ without tissue injury