Collaborative Approaches for Developing Kidney Safety Biomarkers

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Executive Director of the Predictive Safety Testing Consortium (PSTC)
C-Path: A Public-Private Partnership

• Act as a trusted, neutral third party
• Convene scientific consortia of industry, academia, and government for sharing of data/expertise
  ✓ The best science
  ✓ The broadest experience
  ✓ Active consensus building
  ✓ Shared risk and costs

• Enable iterative EMA/FDA/PMDA participation in developing new methods to assess the safety and efficacy of medical products

• Official regulatory endorsement of novel methodologies and drug development tools
Translational Safety Strategies that Accelerate Drug Development

Predictive Safety Testing Consortium (PSTC)

PSTC was formed and officially announced on March 16, 2006.

PSTC brings together pharmaceutical companies to **share and validate innovative safety testing methods** under advisement of the FDA, EMA, and PMDA.

PSTC’s eighteen corporate members have the same goal: to find improved safety testing approaches and methods.
PSTC’s Current Focus

Monitorability of Drug Induced Tissue Injury in Humans

Adverse outcomes in animals

Better Monitoring of Potential Safety Liabilities in Humans

Adverse outcomes in humans

Histopathology

Fluid Based Safety Biomarker

Fluid Based Safety Biomarkers - similar to routine clinical pathology measure that can be used to accurately predict drug induced tissue injury
PSTC’s Current Focus

Is there a need for improved safety biomarkers?
Current biomarker standards do not exist or have significant limitations

<table>
<thead>
<tr>
<th>Organs</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Kidney</strong></td>
<td>Traditional safety biomarkers change only when 50 to 60% of kidney function is lost</td>
</tr>
<tr>
<td><strong>Skeletal Muscle</strong></td>
<td>Current biomarkers are insensitive and nonspecific, as well as poorly predictive</td>
</tr>
<tr>
<td><strong>Liver</strong></td>
<td>Current biomarkers are not sufficiently sensitive and specific, and do not adequately discriminate adaptors from patients at high risk to develop liver failure</td>
</tr>
<tr>
<td><strong>Vascular System</strong></td>
<td>No biomarkers are available for detecting drug-induced vascular injury in humans</td>
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<tr>
<td><strong>Testicular</strong></td>
<td>No circulating biomarkers for seminiferous tubule toxicity</td>
</tr>
<tr>
<td><strong>Cardiac Hypertrophy</strong></td>
<td>Currently no preclinical predictive markers for drug-induced hemodynamic stress leading to changes in cardiac mass</td>
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</tbody>
</table>
Current biomarkers used to monitor kidney safety have significant limitations
• These “gold standard” biomarkers (serum creatinine) change only when 50 to 60% of kidney function is lost

Proposed urinary biomarker panel for drug-induced kidney injury:
1. Clusterin
2. Osteopontin
3. Microalbumin
4. Total Protein
5. N-acetyl-β-(D)-glucosaminidase (NAG)
6. Kidney Injury Molecule-1 (KIM-1)
7. Cystatin-C
8. Neutrophil gelatinase-associated lipocalin (NGAL)
The Critical Path Institute’s Predictive Safety Testing Consortium secures Qualification for 7 novel urine kidney biomarkers as preclinical biomarkers of kidney toxicity
Key Collaborations

The FNIH Biomarkers Consortium Launches Project to Improve Diagnosis of Kidney Injury

Researchers aim to advance acceptance of new biomarkers for monitoring kidney safety in the clinic.

Bethesda, MD (October 25, 2011) – The Foundation for the National Institutes of Health (FNIH) Biomarkers Consortium announced today the launch of a two-year research project to advance the acceptance of new biomarkers designed to detect early kidney injury.

The project is being conducted in collaboration with the Critical Path Institute (C-Path), a public-private partnership founded by the Critical Path Institute (C-Path).

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LEADING US AND EUROPEAN MEDICAL PUBLIC-PRIVATE PARTNERSHIPS ANNOUNCE AGREEMENT

Critical Path Institute and Innovative Medicines Initiative Collaborate on Development of Important New Drug Safety Tests

Tucson, AZ - The Predictive Safety Testing Consortium (PSTC) led by the Critical Path Institute (C-Path) and the Safer and Faster Evidence-based Translation (SAFE-T) consortium sponsored by the Innovative Medicines Initiative (IMI) announced today the
Learn and confirm (progressive) qualification strategy

Nonclinical Phase
- Cisplatin, aminoglycosides, dozens of other renal toxicants were used to demonstrate the superiority of novel biomarkers over sCr for monitoring renal tubular injury (using microscopic histopathology as gold standard)

*Qualification of Seven Biomarkers (2008) and Letter of Support for Two Biomarkers (2014) of Drug-Induced Nephrotoxicity in rats*

Clinical Learning Phase
- Prospective healthy volunteer study
- Archived samples from cisplatin study

*Limited Context of Use Qualification (Submitted in July of 2015)*

Clinical Confirmatory Phase
- Aminoglycoside study in cystic fibrosis patients
- Cisplatin study in cancer patients

*Expanded Context of Use Qualification (Planned submission in 2017)*
Limited Context of Use qualification for drug-induced kidney injury urinary biomarkers:

Claim
A Composite Measure (CM) of urinary biomarkers (all markers) is a qualified safety biomarker of kidney injury response for use in normal healthy volunteer trials supporting early drug development together with monitoring of conventional kidney biomarkers (e.g., serum creatinine and blood urea nitrogen).

Study Population
For use in healthy volunteers only, and for use in subject cohorts not on individual subject basis.
Data for Clinical Learning Phase

Normal healthy volunteer cohort
- N = 80, balanced on gender and age (~40/40, 20-39 years and 40-69 years)
- Longitudinal sample collections over 3 weeks

Cisplatin-treated mesothelioma patient cohort
- N = 58 patients treated with surgical resection and 250 mg/m² intraoperative intrathoracic cisplatin (3% <40 years; 80% males; 62% ≥ stage 2 CKD at baseline)
- Longitudinal sample collections over 6 days
Clinical Learning Phase Data Summary:
Eight (8) Selected Urinary Biomarkers Show Improved Sensitivity Over sCr to Identify Patients Exposed to Cisplatin

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Mesothelioma Patients: Number/N (%) &gt;TSS*</th>
<th>Normal Healthy Volunteers: % &gt;TSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clusterin</td>
<td>19/20 (95.0%)</td>
<td>22/30 (73.3%)</td>
</tr>
<tr>
<td>Osteopontin</td>
<td>20/20 (100.0%)</td>
<td>30/30 (96.8%)</td>
</tr>
<tr>
<td>Microalbumin</td>
<td>20/20 (100.0%)</td>
<td>30/30 (100.0%)</td>
</tr>
<tr>
<td>Total Protein</td>
<td>20/20 (100.0%)</td>
<td>30/30 (100.0%)</td>
</tr>
<tr>
<td>N-acetyl-β-(D)-glucosaminidase</td>
<td>20/20 (100.0%)</td>
<td>27/30 (90.0%)</td>
</tr>
<tr>
<td>Kidney Injury Molecule-1</td>
<td>20/20 (100.0%)</td>
<td>30/30 (100.0%)</td>
</tr>
<tr>
<td>Cystatin-C</td>
<td>19/20 (95%)</td>
<td>22/30 (73.3%)</td>
</tr>
<tr>
<td>Neutrophil gelatinase-associated lipocalin</td>
<td>19/20 (95%)</td>
<td>24/30 (80.0%)</td>
</tr>
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</table>

*TSS = statistically significant threshold.
Expanded Context of Use qualification for drug-induced kidney injury biomarkers:

Claim
Qualified kidney safety biomarkers are proposed to be used together with monitoring of conventional kidney biomarkers (e.g., serum creatinine and blood urea nitrogen), in early clinical drug development research to support conclusions as to whether a drug is likely or unlikely to have caused a mild injury response in the kidney at the tested dose and duration.

Study Population
For use in healthy volunteers and patients with normal kidney function.
Prospective clinical studies

Two prospective studies in patients currently using medications that have the potential to cause pancreatic injury.

- Aminoglycoside study in cystic fibrosis patients
  - Patients (n=100): Adult CF patients, acute pulmonary infection treated with IV tobramycin
  - Controls: Adult CF patients (n=25), acute pulmonary infection treated with IV fluoroquinolone; Adult CF patients (n=25), no pulmonary infection, no treatment

- Cisplatin study in cancer patients
  - Patients (n=100): Patients with head and neck squamous cell carcinoma, and other cancers treated with cisplatin as single agent or part of chemo Tx cocktail
  - Controls (n=50): Cancer patients receiving non-cisplatin chemo Tx treatment, or radiation Tx

✓ Greater diagnostic predictivity compared to serum creatinine as defined by:

1. A formal adjudication procedure
2. A predefined statistical evaluation
The Future State of Biomarker Qualification

Improved definition for the implementation of the qualification process

• Progressive qualification approach – Letter of Support, as well as, Limited and Expanded Context of Use

• Better definition of what is required for qualification – Codified evidentiary considerations (evidentiary standards)

More innovative approaches to biomarker qualification

• Retrospectively collected samples with prospective analysis

• Biomarker data repository for biomarker data from IND studies and qualification projects – What should be considered precompetitive now (2015)?
Thank You

www.c-path.org