



# **Predictive Biomarkers for Nephrotoxicity**

## **Report of the Breakout Session**

**Institute of Medicine Forum on Drug  
Discovery, Development, and Translation**

**October 24, 2008**

# Participants



## Moderators:

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## Panelists:

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# Participants



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# We All Agreed That



- Nothing is certain except death and taxes

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**BUT**

- .. Nephrotoxicity can be deadly
- .. Nephrotoxicity is expensive

# Present State



- .. No validated biomarkers for screening compounds for kidney toxicity in animals
- .. No validated biomarkers for screening compounds for human kidney toxicities, or for demonstrating that kidney toxicities seen in test species are not relevant to humans

## Current Needs

Need renal injury biomarkers qualified for

- regulatory decision making that enable early drug development in animal studies
- early detection of renal injury in humans
- early detection of renal efficacy in humans
- prediction of clinical outcomes in humans

Must Have

Nice to have

# Preferred Future State



- Metabolically competent in vitro screening systems predictive of both human relevant and species specific kidney toxicities
- Resource sparing short study designs incorporating accessible and tissue biomarkers for both rodent and non-rodent toxicology studies that predict kidney toxicity
- Translational qualified biomarkers for monitoring kidney safety in longer animal toxicology studies as well as early human clinical trials

# How do we get there?



## Current Needs

- Need renal injury biomarkers qualified for
- regulatory decision making that enable early drug development in animal studies
  - early detection of renal injury in humans
  - early detection of renal efficacy in humans
  - prediction of clinical outcomes in humans

# Current Efforts and Key Questions



# Consortia and Grant Funded Initiatives Advancing Understanding of the Linkage between Kidney Disease and New Kidney Safety Biomarkers

**AKIN** – The Acute Kidney Injury Network was formed in 2004 with the overall objective of optimizing outcomes in acute kidney injury by leveraging the resources and perspectives of organizations interested in AKI around the globe. This multidisciplinary collaborative network of members representing about 20 key societies in nephrology and critical care, along with additional experts in adult and pediatric AKI, first convened in 2005 to establish a new definition and staging of AKI. During a follow-up meeting in 2006, the group developed a research agenda to test the utility of the AKIN diagnostic and staging criteria to predict patient outcomes in a variety of clinical settings.

**C Path PSTC** – The Critical Path Institute Predictive Safety Testing Consortium was formed in 2006 with 16 companies working with academic advisors, FDA, and EMEA to establish and qualify translational bridging biomarkers for monitoring drug induced kidney injury for regulatory decision-making purposes in both animal toxicology studies and early clinical trials

**ILSI/HESI Kidney Biomarker Committee** – This committee consists of 10 companies collaborating to evaluate promising accessible biomarkers of drug induced kidney toxicities in animals.

**InnoMed** – European Union funded initiative to foster collaborations between pharmaceutical companies and small and medium sized business enterprises (SME's) that can provide technology solutions, services and study sample measurement data to pharmaceutical groups to advance new safety biomarkers

**Intramural NIH Initiatives** – NIDDK Workshop on Assessment of Kidney Function and Damage; etc

**Extramural NIH Funded Academic Centers and Consortia** – Harvard; Cincinnati Children's; TRIBE-AKI (multicenter consortium with Yale as coordinating center), UAB/UCSD O'Brien Core Research Center; etc

# Promising Accessible Biomarkers of Acute Renal Damage or Dysfunction to Complement BUN and Serum Creatinine

<u>Biomarker</u>	<u>Proposed Structural/Functional Interpretations</u>
<b>Albumin</b>	Tubular epithelium functional disturbance biomarker. Small quantities are filtered and efficiently reabsorbed by tubular epithelium.
<b>a-GST</b>	Tubular epithelium cell membrane disruption and cytosol leakage
<b>KIM-1</b>	Tubular epithelium dedifferentiation and regenerative repair response
<b>NGAL</b>	Distal tubule rescue signal to bind deleterious substances, limit damage, promote survival and proliferation
<b>TFF3</b>	Decrease in concentration removes cellular maturation signaling, allowing dedifferentiation
<b>Serum Cystatin C</b>	Functional measure of glomerular filtration and tubular reabsorption.
<b>Urinary Cystatin C</b>	Glomerular damage yields protein overload to lumen to prevent efficient tubular reabsorption process of cystatin C from lumen
<b>b2Mic</b>	Glomerular damage protein overload to tubular lumen prevents efficient tubular epithelium reabsorption of $\beta$ 2Mic from lumen
<b>Proteinuria</b>	Glomerular damage functional marker
<b>L-FABP</b>	Anoxia/ ischemia signal in tubular epithelium and potential oxidative damage signal
<b>Clusterin</b>	Tubular epithelium regenerative repair response
<b>NAG</b>	Brush-border enzyme released when damage occurs to tubular epithelium
<b>IL-18</b>	Tubular epithelium protein reflecting initiation of apoptotic cascades
<b>GGT</b>	Tubular epithelium cell membrane disruption
<b>Others???</b>	

# Current Efforts and Key Questions



- (1) How do we continue to coordinate planning, guide strategy, and set expectations within and across initiatives to optimize the efficiency and impact of biomarker qualification/regulatory acceptance?

# How to proceed with pre-clinical biomarker acceptance/qualification?

- Biomarkers should outperform s creat in animal toxicity study based on histopathology as “gold standard”
- Biomarkers should indicate anatomic site of kidney injury in animal study, because different agents can affect different nephron segments
- Harmonized lexicon for histopathology
- Understand what biomarker combinations are telling us regarding stage of kidney injury or repair
- Have mechanisms for standardized preclinical data accumulation, sharing and interpretation rules via consortia
- Have preliminary data indicating sensitivity of the biomarker combination in human studies (predictive of kidney damage and short-term clinical outcomes)

# Current Efforts and Key Questions



- (2) How can we advance better biomarkers in the clinic when the current gold standard is flawed, and avoid debate over “false positives”, “prodromals”, or flawed standards? How do we access clinical samples?

# Alternative Gold Standards and Strategies

- .. Use human biopsy histopathology for correlation with biomarkers
  - n Patients with hematuria and glomerular disease
  - n Protocol transplant biopsies
- .. Use standardized national bio-repositories for comparing biomarkers from ongoing clinical trials – and we need to access de-identified samples and share data
  - n NIH public-private partnership office can coordinate this
  - n Need a system for industry to share clinical data

# Current Efforts and Key Questions

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- .. (3) Can we structure incentives and freedom to operate to deploy investigations of new safety biomarkers in regulated studies that support new product development?
  - n Incentives for exploratory studies?
  - n Incentives for negative controls?
  - n Need open dialogue between industry and regulatory agencies
  - n FDA-NIH partnership to consider funding for research on biomarker development for monitoring drug safety and toxicity

# Current Efforts and Key Questions



- .. (4) How can we foster the development of in vitro and other screening model systems to screen compounds very early in or out of the drug development pipeline?
  - n Cell culture systems not very reliable
  - n Embryonic stem cells and zebra fish models are promising
  - n Additional systems may emerge from academia, but partnership with industry and NIH can accelerate development of in vitro systems for nephrotoxicity

**Thanks for your attention!**



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