HESI Technical Committee on Application of Biomarkers of Toxicity

HESI Assembly of Members Meeting
January 19, 2009
Tucson, AZ

Biomarkers Committee Mission

- Advance the scientific basis for the development and application of biomarkers of target organ toxicity

- Provide a scientific forum for building consensus regarding how to apply and reach acceptance of biomarkers of toxicity in risk assessment

Biomarkers Committee 2008 Participation

Industry

Abbott Laboratories
Allergan Inc.
Amgen Inc.
Astellas Pharma Inc.
AstraZeneca AB
Bayer HealthCare Pharmaceuticals
Biogen Idec MA Inc.
Boehringer Ingelheim GmbH
Bristol-Myers Squibb Company
GlaxoSmithKline
Hoffman-La Roche Inc.
Johnson & Johnson Pharmaceuticals
Pfizer, Inc.
sanofi-aventis

Public Participation
(Government and Academia)

University of Arizona
University of Minnesota
Liverpool John Moores University
US Environmental Protection Agency
US Food and Drug Administration
US National Institute of Environmental Health Sciences

Biomarkers Committee Structure

Biomarkers of Nephrotoxicity Project Team

- Chair – Dr. Ernie Harpur, sanofi-aventis
- Vice-Chair – Dr. Sven Beushausen, Pfizer

Biomarkers of Cardiac Toxicity Project Team

- Chair – Dr. Malcolm York, GSK
- Vice-Chair – Dr. Dana Walker, BMS

HESI Staff: Syril Pettit, Cyndi Nobles

Renal BM Project Team (PT) Goals

- Conduct multi-lab studies to evaluate a panel of potential nephrotoxicity biomarkers (*initially α-GST, μ-GST, RPA-1, clusterin*) for their utility in assessing drug-induced injury to the kidney in preclinical safety studies

- Through a process of validation, establish the scientific and regulatory acceptance the new biomarkers –
  - FDA/EMEA *Voluntary Biomarker Qualification Process Participant*

Conclusions of Renal BM PT

In studies in rodents, as compared with existing BMs (BUN, Scr, protein, GGT, and NAG)

- α-GST is a more sensitive and specific BM of proximal tubular injury. *Available clinical data suggest this can be used as a bridging marker.*
- RPA-1 is a identified as a sensitive and highly specific BM of collecting duct injury. *No human equivalent yet identified.*
- Clusterin offers promise as a general BM of tubular injury, particularly when regeneration is present

Participant in FDA/EMEA BQR Process

- May 2008: Submitted qualification report to FDA/EMEA on May 1, 2008

- July 2008: Met w/FDA and EMEA in London and White Oak, MD to discuss submission

- December 2008: Submitted formal written response and additional information per FDA-EMEA requests and queries

- Further comments and/or decision on qualification anticipated in early 2009

Renal BM PT
Other 2008 Activities

- Six presentations at international meetings: SOT (Seattle), DIA (Boston), ACT (Tucson), AECCP (Barcelona), Safety Biomarker Forum (London), Innomed PredTox (Basel),

- Manuscripts in preparation for submission to peer review process in 1Q 2009

Renal BM PT 2009 Plans

- Complete BQR process
- Conduct additional studies to confirm and expand context of current studies (e.g. organ specificity, prognostic v diagnostic, reversibility, sex effect, longer term administration, additional BMs and multiplexed assays, use in dog)

  (Planned studies will address the points underlined)

- Ensure synergies with other related programs (e.g. C-Path PSTC, IMI) to maximize contributions to the field – will be particularly important with regard to clinical translation

Cardiac BM Project Team

- Primary focus on cardiac troponin as a marker of cardiac injury
  - Performed Analytical Validation - of selected cTn assays, established degree of assay cross-reactivity, linearity, detection limit and precision for rat, dog and monkey
  - Manuscript Published Dec 08: *Analytical Characteristics of Commercial Cardiac Troponin I and T Immunoassays In Serum From Rats, Dog and Monkeys Subjected to Acute Myocardial Injury – Apple FS, Murakami MM, Ler R, Walker D, York M; HESI Technical Committee of Biomarkers Working Group on Cardiac Troponins. Clin Chem. 2008 Dec;54(12):1982-9. Epub 2008 Oct 9.*

- Biological Qualification - establish diagnostic window for cTn with drug-induced cardiomyocyte injury and correlate with histopath.
  - Isoproterenol study in rodents. *Manuscript in progress.*
  - Doxorubicin study co-sponsored with HESI Genomics. cTn analysis relative to histopath and gene expression underway. *Manuscripts to be developed in 2009*

Cardiac BM Project Team
Other 2008 Activities

- February 2008: HESI Workshop on Bridging Preclinical-Clinical Evaluation of Drug-Induced Cardiotoxicity.
  - Manuscript to be finalized this month, to *American Heart Journal*

- October 2008: Co-organizers/participants in HESI- Duke Cardiac Safety Research Consortium 'Cardiac Safety Think Tank' Meeting, Bethesda, MD.
  - HESI-CSRC Manuscript on workshop discussions in progress

- November 2008: FDA Grand Rounds on Cardiac Troponin. Committee Chair presented overview of HESI research and future activities to Agency staff.

Cardiac BM PT 2009 Plans

- Finalize manuscripts
- Complete analysis of doxorubicin study data including additional sample evaluation with 'ultra-sensitive' assays
- Explore proposal to create preclinical cardiac troponin 'data bank' in collaboration with FDA
- Transfer in 2009 from the Biomarkers Committee to become an integral part of the HESI Committee on Cardiac Safety