Genomic Applications in Safety Studies - Case Study Workshop

Executive Summary

Genome-wide expression profiling and other genomics-based technologies are increasingly being used during development and characterization of candidate compounds in the pharmaceutical and agrochemical industries. In most cases, genomics technologies are used to predict and/or analyze the mechanism of drug-related toxicity and/or pathology (*i.e.*, toxicogenomics). The increasing use of these technologies has created an imperative, recognized by the Health and Environmental Sciences Institute (HESI)[1,2], to bring scientists together to share and further promote successful use and implementation of toxicogenomics, and its integration into weight-of-evidence approaches for safety and risk assessment of candidate pharmaceutical and chemical compounds.

To this end, HESI organized a workshop entitled *Genomics Applications in Safety Studies - a Case Study Workshop* on October 27-28, 2008 in Arlington, Virginia (See workshop program in Attachment 2). The goals of the workshop were: 1) to provide a forum for presenting toxicogenomics case studies; 2) to assess the scientific impact of toxicogenomics on the pharmaceutical and chemical industries and on regulatory and government research activities; and 3) to identify gaps, resources and future directions for application of genomics technologies in risk assessment and safety studies. This document summarizes the main workshop outcomes.

Approximately 90 participants, representing stakeholders in the bio-pharmaceutical agrochemical industries, government and regulatory agencies gathered together at this workshop to assess the state-of-the-science of toxicogenomics in their industries and organizations. The consensus emerging at the workshop is that toxicogenomics applications are appropriate and valuable in the context of a weight-of-evidence approach for risk assessment of pharmaceutical and other compounds. In this context, toxicogenomics data are often used to de-risk a compound for future development, or conversely, to flag a compound for a potentially unacceptable margin-of-safety or risk-benefit ratio at later developmental stages. Current practices in use of toxicogenics-based approaches, as assessed at this workshop, are summarized in Box 1.

There was some discordance with regard to the most advantageous stage of drug development at which toxicogenomics-based approaches should be applied. This question is at least partly related to the issue of how to best use limited R&D resources: is it most valuable to analyze toxicogenomics signatures post lead-optimization in livers of treated animals in parallel with histopathological analysis of the same animals? Or, is it more useful and possibly more cost-effective to carry out 7 or 14 d *in vivo* toxicogenomics studies during lead-optimization, when one might include more candidate compounds, and might not collect histopathological data in parallel? Another unresolved question emerging at the workshop is the relative value of *in vitro* toxicogenomics studies in rat and/or human primary hepatocytes *vs. in vivo* studies for assessing hepatotoxicity. Additional development and refinement of *in vitro* toxicogenomics-based approaches are needed before they can be used with confidence throughout the industry.

Case studies at this workshop focused primarily on toxicogenomics as a predictive tool for assessing potential hepatotoxicity or genotoxicity. Hepatotoxicity has been and remains a primary focus of many toxicogenomics studies, while toxicogenomics-based prediction of genotoxicity was discussed at this workshop as the possible next area ripe for development. This area is important for many reasons, not the least because of the magnitude of cancer as a public health burden, the time- and cost-intensive nature of the 2 year rodent bioassay, and the relatively high presumed false-positive rate associated with the traditional genotoxicity test battery.

This workshop provided an opportunity for stakeholders to share experiences regarding uses of genomics technology in industry and the regulatory community, and to explore the potential increased impact of this technology. The Genomics Committee will further review the workshop discussions to help guide development of future projects.

Box 1

- Toxicogenomics is being used opportunistically in the context of a "weight-of-evidence" approach during development and characterization of pharmaceuticals and chemicals.
- Toxicogenomics is being used routinely in development of pharmaceuticals and chemicals to predict and analyze mechanisms of hepatotoxicity.
- There is controversy over the relative value of *in vitro* vs *in vivo* toxicogenomics assays for predicting and analyzing hepatotoxicity.
- Toxicogenomics is being explored as a tool for interpreting existing genotoxicity assays, prioritizing compounds for genotoxicity testing and streamlining the prediction of carcinogenicity.
- In some cases, stronger management support for and willingness to allocate resources for increased use of toxicogenomics is still needed.
- There is strong support for collaborative efforts to promote toxicogenomics as a tool in development and characterization of pharmaceuticals and chemicals (for example, tissue banking, database development, data sharing etc.).
- Toxicogenomics is not currently being used routinely in regulatory submissions for pharmaceuticals and chemicals. However, regulatory agencies are receptive to use of toxicogenomics during biomarker qualification and in support of applications for regulatory approval of novel compounds.
- Successful use of toxicogenomics requires cultivation and retention of a team of knowledgeable, experienced, innovative and creative scientists, especially pathologists and bioinformaticians.

[1-] The International Life Sciences Institute (ILSI) is a nonprofit, worldwide foundation, whose goal is to address scientific issues relating to nutrition, food safety, toxicology, risk assessment, and the environment. ILSI is strongly committed to involving all relevant stakeholders in resolving these issues, inviting scientists from academia, government, and the pharmaceutical and agrochemical industries to participate in all ILSI programs and initiatives. Within ILSI, the Health and Environmental Sciences Institute (HESI) specifically promotes scientific research and educational programs on environmentally-related human health issues.

[2-] In mid-1999, HESI formed the Committee on the Application of Genomics to Mechanism-Based Risk Assessment, whose goal is to develop a collaborative scientific program to address issues, challenges, and opportunities in the emerging field of toxicogenomics. The Committee includes experts and advisors from academia and government agencies, and representatives from over 20 pharmaceutical, agrochemical, chemical and consumer products' companies. The Committee has designed and implemented collaborative projects using genomics technologies to analyze mechanisms of hepatotoxicity, nephrotoxicity and genotoxicity. These projects have helped define the issues and overcome the challenges of using these emerging technologies, such as identifying sources of biological and technical variation and collecting, storing, analyzing and interpreting voluminous genomics-based datasets.

Attachment 2

Genomic Applications in Safety Studies - Case Study Workshop
Organized by the HESI Committee on Application of Genomics in Risk Assessment
October 27-28, 2008
Arlington, Virginia
Palomar Hotel Arlington

Agenda

October 27, 2008

12:00P – 12:30P **REGISTRATION AND POSTER SET-UP**

12:30P – 1:00P **Introduction and Welcome – Dr. Cynthia Afshari, Amgen**

1:00P – 1:30P **Current Industry Needs for Genomics in the Safety Assessment Toolbox – Dr. Bruce Car, Bristol-Myers Squibb**

1:30P – 3:45P **Session A: Case Studies in Investigative Applications (Pharmaceutical)**

Discussion leaders: Dr. David Jacobsen-Kram, FDA and Dr. Ruth Lightfoot-Dunn, Amgen

All speakers in this session will address the following: What was the question to be answered with this genomics application and was the goal achieved? Was the answer a "stand alone" derived from the transcript/genomics analysis or did it require integration with other data? Was follow-up with additional experiments needed to fully answer the question or to confirm the answer?

Presenters: *15 minute presentation plus 10 min for Q&A*
Dr. Hisham Hamadeh, Amgen
Dr. Jiri Aubrecht, Pfizer
Dr. Jonathan Tugwood, AstraZeneca
Dr. Russell Thomas, Hamner Institute
Dr. Michael Lawton, Pfizer

3:45P – 4:00P **Break**

4:00P – 6:05P **Session B: Case Studies in Investigative/Screening Applications (Chemical)**

Discussion leaders: Dr. William Benson, EPA and Dr. Rick Paules, NIEHS

Presenters: *15 minute presentation plus 10 min for Q&A*
Dr. Darrell Boverhoff, Dow Chemical Company
Dr. Doug Wolf, U.S. Environmental Protection Agency
Dr. Rick Irwin, National Toxicology Program
Dr. Jos Kleinjans, Universiteit Maastricht

6:05P – 7:15P **Poster Session and Reception**

Agenda (Cont'd)

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October 28, 2008

7:30A **Continental Breakfast**

7:50A Reconvene Session and Welcome

8:00A - 10:10A **Session C: Case Studies in Predictive/Screening Applications – (Pharmaceutical)**

Discussion leaders: Dr. Bruce Car, BMS and Dr. James MacDonald, Schering-Plough

All presenters in this session will address the following in the context of their case study:

1. Are Genomics and the cases shown routinely applied within your organization? To some or all of your programs? Where in Lead Optimization/development?
2. Do you apply genomics in vitro or in vivo?
3. Do you use whole genome arrays or a partial genome (via arrays or other transcript assessment platform)?
4. What is your overall goal for your screen/ deliverable to project teams?

Presenters: *15 minute presentation plus 10 min for Q&A*
Dr. Eric Blomme, Abbott
Dr. Craig Thomas, Lilly
Dr. Patrick Wier, GlaxoSmithKline
Dr. Jean-Christophe Hoflack, Roche
Dr. Hiroyoshi Toyoshiba, Takeda Pharmaceutical Company Ltd.

10:10A – 10:30A **BREAK**

10:30A – 11:50A **Session D: Regulatory Experience and Case Studies**

Discussion Leader: Dr. Frank Sistare, Merck and Dr. James Stevens, Lilly

Presenters: (15 min summary and 5 min discussion each)
Dr. Susan Euling, U.S. Environmental Protection Agency
Dr. Federico Goodsaid, U.S. Food and Drug Administration
Dr. David Jacobson-Kram, U.S. Food and Drug Administration
Dr. Isabel Viera, Safety Working Party, European Medicines Evaluation Agency

11:50A – 12:10P **Pick up box lunches in foyer**

12:10P – 1:00P **Lunchtime Seminar: The Emerging Science of Safety – Special Guest, Dr. Janet Woodcock, Director, Center for Drug Evaluation and Research, U.S. Food and Drug Administration**

1:00P – 3:30P **Session E: Additional Case Studies**

Discussion Leaders: Dr. Lois Lehman-McKeeman, BMS and Dr. Nathaniel Collins, Schering-Plough

1:00P – 1:50P Session E1: Case Studies in Adverse Events and Genetic Variation

Dr. Allen Roses, Duke University
Dr. Paul Watkins, University of North Carolina

1:50P – 2:40P Session E2: Case Studies in Cross-Species Differences

Dr. Mark Fielden, Roche
Dr. William Foster, BMS

2:40P – 3:05P Session E3: Case Study(ies) on Application of Genomics to Understand a Safety Aspect of Biotherapeutics

Dr. Matthew Cooper, Roche

3:05P – 3:30P BREAK

3:30P – 4:20P Session E4: Case Study(ies) Highlighting the Impact of Non-Genomics (i.e. Proteomic, Metabonomic) Technologies to Solving a Problem in Safety Assessment (Pharmaceutical)

Dr. Donald Robertson, Bristol-Myers Squibb
Dr. Jon Lyon, GlaxoSmithKline

4:20P – 5:00P Session F: Summary Session and Discussion Panel

This session will summarize overall areas of focus: progresses and success, limitations and barriers, areas for future research, and areas for future regulatory-industry dialogue/activity

Panelists

Dr. Lois Lehman-McKeeman, Bristol-Myers Squibb
Dr. Frank Sistare, Merck
Dr. William Benson, U.S. Environmental Protection Agency
Dr. John Leighton, U.S. Food and Drug Administration
Dr. Ruth Lightfoot-Dunn, Amgen
Dr. James MacDonald, Schering-Plough
Dr. James Stevens, Lilly

5:00P – 5:15P Closing Remarks and Adjourn