

Guest Editorial

Toxicogenomics in Risk Assessment: Communicating the Challenges

In 1999 the membership of the International Life Sciences Institute (ILSI) Health and Environmental Sciences Institute (HESI) formed a multisector consortium to address challenges associated with the integration of genomics data into risk assessment (Pennie et al. 2004). Following its formation, the HESI Committee on the Application of Genomics to Mechanism-Based Risk Assessment identified several key hurdles. These included a lack of publicly available toxicogenomics databases, a lack of validation of available technologies, questions concerning the comparability of different technical platforms and how transcription products relate to toxicity, and uncertain regulatory applications.

In 2004 we have seen considerable progress in many of the areas mentioned above, particularly in our technical ability to execute microarrays and to analyze and interpret the resultant data. The experimental program of the HESI Genomics Committee clearly demonstrated that it is possible to replicate data on biologic pathways across laboratories and technical platforms (Kramer et al. 2004; Ulrich et al. 2004). The committee's work also revealed the need to interpret modulations in gene expression on microarrays in the context of a broader biologic data set (e.g., clinical chemistry, histopathology). Additionally, within the United States, the recent release of draft regulatory guidance from the U.S. Food and Drug Administration (FDA 2003) on the use of pharmacogenomics data in risk assessment and the release of a white paper from the U.S. Environmental Protection Agency (U.S. EPA 2004) on potential regulatory applications of genomics data have further focused potential applications. However, the routine application of genomics to preclinical risk assessment has not yet been accepted universally. Why?

The efforts of the HESI Committee on Genomics regarding experimental collaboration and toxicogenomics database development (Mattes et al. 2004) suggest that some of the greatest outstanding challenges relate to effective communication across key user groups. It is critical that regulated industries share with the regulatory community the focus of their current approaches to the use of genomics. For example, are microarray data used primarily for early screening or for researching mechanisms of toxicity and under what circumstances? Additionally, open information exchange regarding typical means of data analysis and presentation is needed. This exchange, which has been initiated via several multisector forums including HESI, will help ensure that a common understanding of the technology's practical strengths and limitations is reached and allow genomics to be applied more effectively to safety assessment. Discussions concerning the interpretation of patterns of change in gene expression in relation to other biologic end points will provide critical context for determining the suitability of a data set for risk evaluation. Consensus as to when changes in gene expression via microarray represent definitive



Syril D. Pettit

biomarkers of effect is also needed. Until these conditions are clarified, the utility of genomics for classifying effects of concern will remain debatable.

The risk assessment community is also striving both to harness the collective power of publicly available data sets and to facilitate exchange of single data sets for safety evaluation. As such, numerous formats for the capture and exchange of microarray and toxicology data have become available and/or are under development (Mattes et al. 2004). Diversity of approach is not in itself problematic and clearly has its benefits. However, the development of flexible and comprehensible data exchange platforms that meet the needs of multiple user groups is essential for routine exchange of toxicogenomics data.

The HESI Committee on Genomics looks forward to an ongoing role as a multi-stakeholder consortium committed to facilitating discussion on the scientifically sound use of genomics for risk assessment.

Syril D. Pettit

Health and Environmental Sciences Institute
International Life Sciences Institute
Washington, DC
E-mail: spettit@ilsii.org

Syril D. Pettit is a senior scientific program manager at the ILSI Health and Environmental Sciences Institute where she has managed collaborative science programs since 2000.

REFERENCES

- FDA. 2003. Draft. Guidance for Industry. Pharmacogenomic Data Submissions. Draft Guidance. Washington, DC: Food and Drug Administration. Available: www.fda.gov/cder/guidance/5900dft.pdf [accessed 26 July 2004].
- Kramer JA, Pettit SD, Amin RP, Bertram TA, Car B, Cunningham M, et al. 2004. Overview of the application of transcription profiling using selected nephrotoxicants for toxicology assessment. *Environ Health Perspect* 112:460–464.
- Mattes WB, Pettit SD, Sansone S-A, Bushel PR, Waters MD. 2004. Database development in toxicogenomics: issues and efforts. *Environ Health Perspect* 112:495–505.
- Pennie W, Pettit SD, Lord PG. 2004. Toxicogenomics in risk assessment: an overview of an HESI collaborative research program. *Environ Health Perspect* 112:417–419.
- Ulrich RG, Rockett JC, Gibson GG, Pettit S. 2004. Overview of an interlaboratory collaboration on evaluating the effects of model hepatotoxicants on hepatic gene expression. *Environ Health Perspect* 112:423–427.
- U.S. EPA. 2004. Draft. Potential Implication of Genomics for Regulatory and Risk Assessment Applications at EPA. Washington, DC: U.S. Environmental Protection Agency, Science Policy Council.

“ . . . the identification, verification, and validation of biomarkers are critical components of every pharmacogenomics, as well as toxicogenomics, study of cases in regulatory decision making.”

Guest Editorial

Regulatory Acceptance of Toxicogenomics Data

Early identification of toxicologic side effects of a drug candidate is critical to an efficient drug discovery and development process. Toxicogenomics, the marriage of data-rich genomics approaches with traditional toxicologic end point evaluation combined with increasingly powerful *in silico* modeling approaches, promises to accelerate this process. The advent of parallel experimental platforms, for example, DNA microarrays, has enabled us to gain insight into complex biologic responses to drugs. The challenge is to analyze and correctly interpret these large data sets. Currently, no common standards exist for such data even though attempts are being made to streamline and standardize the presentation of the information. These efforts include ArrayExpress infrastructure for microarray data (<http://www.ebi.ac.uk/arrayexpress>), Minimum Information About a Microarray Experiment (<http://www.mged.org/Workgroups/MIAME/miame.html>), and MicroArray Gene Expression (MAGE) markup language ([http://www.mged.org; http://www.omg.org/technology/documents/formal/gene_expression.htm](http://www.mged.org;http://www.omg.org/technology/documents/formal/gene_expression.htm)).

The creation of vast amounts of genomics and toxicogenomics data has sparked the development of novel systems to handle this type of information. Ultimately, the success of a toxicogenomics approach in drug development depends on our ability to interpret the data in relation to existing information (e.g., screening of a drug-induced gene expression fingerprint against a database containing drug-related gene expression toxicity profiles). It is critical that interdisciplinary information (chemistry, biochemistry, genetic, genomics, clinical) be integrated into the same data warehouse. Incorporating toxicogenomics data into this approach, which is often referred to as systems biology, will help us understand in much more depth how cells maintain homeostasis and how organisms respond to drug exposure at the molecular level.

The mission of the U.S. Food and Drug Administration (FDA) states that the agency “. . . is responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable. . . .” (FDA 2004). Former agency commissioner Mark McClellan stated that “the FDA priority is facilitating the use of pharmacogenetics-driven treatments” (Salerno and Lesko 2004). The FDA has recently issued a draft, “Guidance for Industry: Pharmacogenomic Data Submissions” (FDA 2003), and has held workshops to discuss issues related to pharmacogenomics data submissions (Salerno and Lesko 2004a, 2004b; Leighton et al. 2004; Ruaño et al. 2004; Trepicchio et al. 2004). This guidance is being revised on the basis of public comments, and a final guidance should be issued later this year. Many principles found in this guidance apply to toxicogenomics studies. In particular, the identification, evaluation, and validation of biomarkers are critical components of every pharmacogenomics, as well as toxicogenomics, study of cases in regulatory decision making.



Felix W. Frueh



Shiew-Mei Huang

The guidance is general and includes examples of genetic and genomic biomarkers: a *CYP2D6* (cytochrome P450 2D6) mutation versus an increase in HER2 (human epidermal growth factor receptor 2) expression can be viewed as genetic and genomic biomarkers, respectively. However, it is anticipated that future data submissions will contain many more complex gene expression profiles and large-scale single nucleotide polymorphism maps (e.g., from whole genome scans), which will present new challenges to define the analytical and clinical validity of such new and highly complex biomarker sets. The guidance represents the FDA's current view on pharmacogenomics and what the agency believes are the scientific grounds for evaluating such information as it relates to voluntary versus required submission of data.

What are the next steps? Regulators have been criticized for the lack of guidance in the new era of genomics-based drug development. In addition to the guidance on pharmacogenomics data submissions (FDA 2003), the FDA is embarking on a new guidance initiative for the co-development of pharmacogenomics-based drugs and biologic products and the diagnostic tests necessary for therapeutic decision making. Recently, the FDA and the Drug Information Association (DIA) sponsored a pharmacogenomics workshop (FDA/DIA 2004). The purpose of the workshop was to identify issues in the development of pharmacogenomics-based combination products. We hope to see the base of pharmacogenomics knowledge grow and expand, and we look forward to the use of this information in the drug discovery and regulatory evaluation processes. We expect that not only the novel scientific but also the newly created regulatory tools such as voluntary submissions of genomics data will provide the means by which genomics-based research can excel in advancing public health and drug development.

Felix W. Frueh
Shiew-Mei Huang
Lawrence J. Lesko

Office of Clinical Pharmacology and Biopharmaceutics
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Rockville, Maryland
E-mail: huangs@cder.fda.gov

Felix W. Frueh is Associate Director for Genomics, OCPB, CDER, FDA. He directs the Interdisciplinary Pharmacogenomics Review Group (IPRG) responsible for the review of genomic data submissions to the FDA. He is a member of the FDA Pharmacogenomics Working Group and chairs the Pharmacogenomics Focus Group of the American Association for Pharmaceutical Scientists (AAPS).

Shiew-Mei Huang is Deputy Office Director for Science, OCPB, CDER, FDA. She currently chairs an FDA drug interaction working group and an OCPB good review practices working group and is a member of the FDA Pharmacogenomics, FDA Ethnicity/Race, and CDER QT Working Groups, and the CDER Research Coordinating Committee.

Lawrence J. Lesko is director, OCPB, CDER, FDA. He chairs the FDA Pharmacogenomics Working Group and is a key member of the FDA Critical Path Initiatives. Note: Photograph for L.J. Lesko was unavailable.

REFERENCES

- FDA. 2003. Draft. Guidance for Industry. Pharmacogenomic Data Submissions. Draft Guidance. Washington, DC: Food and Drug Administration. Available: www.fda.gov/cder/guidance/5900dft.pdf [accessed 26 July 2004].
- FDA. 2004. FDA Mission Statement. 2004. Washington, DC: U.S. Food and Drug Administration. Available: <http://www.fda.gov/opacom/morechoices/mission.html> [accessed 26 July 2004].
- FDA/DIA. 2004. Co-Development of Drug, Biological and Device Products, 29 July 2004, Arlington, VA. Washington, DC: U.S. Food and Drug Administration/Horsham, PA: Drug Information Association. Available: <http://www.diahome.org/Content/Events/04040.pdf> [accessed 26 July 2004].
- Leighton JK, DeGeorge J, Jacobson-Kram D, MacGregor J, Mendrick D, Worobec A. 2004. Pharmacogenomic data submissions to the FDA: non-clinical case studies. *Pharmacogenomics* 5(5):507–511.
- Ruaño G, Collins JM, Dorner AJ, Wang S-J, Guerciolini R, Huang S-M. 2004. Pharmacogenomic data submissions to the FDA: clinical pharmacology case studies. *Pharmacogenomics* 5(5):513–517.
- Salerno RA, Lesko LJ. 2004a. Pharmacogenomic data: FDA voluntary and required submission guidance. *Pharmacogenomics* 5(5):503–505.
- Salerno RA, Lesko LJ. 2004b. Pharmacogenomics in drug development and regulatory decision-making: the Genomic Data Submission (GDS) proposal. *Pharmacogenomics* 5(1):25–30.
- Trpicchio WL, Williams GA, Essayan D, Hall ST, Harty LC, Shaw PM, et al. 2004. Pharmacogenomic data submissions to the FDA: clinical case studies. *Pharmacogenomics* 5(5):519–524.

Note from the Editor Addressing Applications of Genomics Data

The two editorials in this issue of *EHP* address the application of toxicogenomics data in the risk assessment and regulatory processes. Also addressing these issues is the National Research Council/National Academy of Sciences Committee on Emerging Issues and Data on Environmental Contaminants. (<http://dels.nas.edu/emergingissues/index.asp>). This committee, formed at the request of the National Institute of Environmental Health Sciences (NIEHS), provides a public forum for discussing emerging issues in environmental toxicology.

The committee comprises experts from academia, industry, and public interest groups whose specialties include toxicology, toxicogenomics, genetics, bioinformatics, risk assessment, medical ethics, epidemiology, communications, public health. In addition, a U.S. federal government liaison group has been created to work with the committee with representatives from the NIEHS, the Centers for Disease Control and Prevention, the Environmental Protection Agency, the Food and Drug Administration, the

Department of Agriculture, the Department of Energy, the Occupational Safety and Health Administration, the Department of Defense, and the Department of Transportation.

A subcommittee is being formed to write a “Consensus Report on the Applications of Toxicogenomic Technologies to Predictive Toxicology.” This report will highlight how the study of gene and protein activities and other biological processes can improve the characterization of toxic substances and their potential risks. Ultimately, this report should show how major new or anticipated uses of these technologies could improve the protection of public health and the environment.

Thomas J. Goehl
Editor-in-Chief, *EHP*
NIEHS
National Institutes of Health
Department of Health and Human Services
Research Triangle Park, North Carolina
E-mail: goehl@niehs.nih.gov