# Toxicogenomic Applications to Drug Risk Assessment


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Over the past several years, genomic technologies have evolved that enable the simultaneous analysis of the expression of hundreds to thousands of genes. This capability has completely changed the types of questions and the quality of information that can be queried by biomedical scientists. The functional status of a living cell can be characterized at the molecular level by its gene expression patterns. Cells belonging to different tissues and organs, cells in various developmental stages, cells in different metabolic states, cells under the influence of specific chemicals (whether natural or synthetic, endogenous or exogenous), cells within a diseased tissue or tumor—all may differ by their gene expression patterns at any given point in time.

Of the various applications of genomic technologies, toxicology is one of the most pragmatic in terms of its role in the safety assessment of new therapeutic candidates. The analysis and evaluation of gene and protein expression changes that modulate toxic responses has been named toxicogenomics and toxicoproteomics, respectively. These emerging disciplines promise to revolutionize the field of toxicology by aiding and supplementing our mechanistic understanding of how drug treatments in animals and humans induce toxic insults in one or more tissues or organs. With the possible exception of very rapid cell death, it is believed that gene expression changes underlie all drug-induced toxic events. The question is will analysis of drug-induced gene expression changes lead to a better understanding of the mechanism of toxicity? And if so, can investigators use this knowledge to design a safer drug without compromising the drug's beneficial (therapeutic) effects? Will genomic analysis lead to the identification of useful biomarkers of toxicity, i.e., a biological signal that can be measured in patients that will accurately report or, better yet, predict the onset of drug-induced toxicity? Will genomic analysis lead to gene expression or protein expression patterns that become the "signature" of toxic potential for that particular drug? If the answer is "yes," then can genomic patterns become useful screens applied in the early drug discovery stages, leading to less toxic "lead candidates" that enter drug development? These questions and others are being intensely and actively investigated by nearly every major pharmaceutical and biotechnology company as well as by the U.S. Food and Drug Administration (FDA), the National Institute of Environmental Health Sciences, and numerous academic laboratories.

Over the past several years, a number of forums involving the pharmaceutical and biotechnology industries, regulatory agencies, and academia have been organized to address some of these challenges. In mid-1999 the Health and Environmental Sciences Institute (HESI) of the International Life Sciences Institute (ILSI) (http://hesi.ilsi.org/) formed a project committee to develop a collaborative scientific program to identify and address some of the key issues arising from the emerging application of toxicogenomics to drug safety risk assessment. The investigational studies conducted and reported by this consortium (Hamadeh et al. 2002; ILSI/HESI 2003) created a path for several other forums focused on this and related topics. An active HESI consortium now exists for the search, characterization, and validation of biomarkers of drug-induced toxicity. Immediate goals include the design and conduct of studies that will identify early predictive biomarkers of nephrotoxicity, cardiotoxicity, and testicular toxicity.

It is now apparent that one major application of toxicogenomics in drug development is the identification and characterization of early predictive biomarkers of toxicity. More sensitive and specific biomarkers will contribute not only to the understanding of the mechnisms involved in drug-induced toxic responses but also to improving human risk assessment that is fundamental to the drug approval process by the FDA or other regulatory agencies. Many of the conventional biomarkers used in preclinical drug safety studies are either insensitive, nonspecific, or they appear late in the pathogenesis of the lesion and, as such, qualify only as reporters or indicators of toxicity. Other criticisms of conventional biomarkers include their noninvasive accessibility, their limited species specificity, and their relevance to human risk. Genomic-derived biomarkers have the potential of appearing early in the pathogenesis of the lesion, possibly serving as predictors as opposed to indicators of toxicity (Goodsaid 2003; Guerreiro et al. 2003). In addition, genomic technologies have the potential of expanding accessible biomarkers across test species in toxicology studies. One of the major goals is to discover biomarkers that bridge preclinical and clinical studies.

A variety of recent forums have focused on the issue of genomic data submission to support human risk assessment. The FDA and PhRMA (Pharmaceutical Research and Manufacturers of America) have sponsored workshops focused on the generation of guidelines for genomic data submission. The inaugural meeting, held spring 2002, created the framework for several follow-up meetings on this topic. The FDA perspective is that genomic data will enrich new drug applications, and the agency has encouraged sponsors to submit genomic data in drug submissions under a "safe harbor" provision. The majority of sponsors are concerned that the science of genomics is still developing and that the FDA is not prepared to review or interpret genomics data. The fear is that submission of genomics data will result in significant differences in data interpretation, resulting in many questions that will delay FDA approvals. The Drug Information Association (DIA) in collaboration with the FDA, PhRMA, the Biotechnology Industry Organization (BIO), and the companies represented by the Pharmacogenomics Working Group (PWG) has scheduled a workshop 13–14 November 2003 that will discuss and debate the draft FDA guidelines titled "The Genomic Data Submission (GDS) Proposal" (http://www.diahome.org).

Within the context of pharmaceutical drug development, the ultimate payoff for toxicogenomics and toxicoproteomics can be enormous. However, we are not ready for "prime time." Many challenges must be met to ensure scientific valid and appropriate incorporation of these technologies into product development, product evaluation, product regulation, and ultimately, medical practice. From a regulatory viewpoint, several critical issues will likely affect the level of scientific scrutiny of genomic-derived data. Key factors include the stage or stages of drug development at which these technologies are applied. The FDA emphasized that

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the level and rigor of scientific scrutiny of data will depend on when in drug development these methods are applied and how the resultant data intend to be used. The outcome of the DIA–FDA–PhRMA–BIO–PWG workshop in November should help clarify many impending issues and pave the way for new technological applications that can improve the risk assessment process.

A tremendous effort of everyone will be needed to move rationally in the direction of achieving scientific credibility, followed by regulatory and scientific consensus of how and when to apply genomic data to drug development and the approval of new medicines. The payoffs include a better understanding of human diseases, safer and more effective drugs to treat diseases, and more efficient and quicker development time for producing and marketing new therapeutic agents.

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