Meeting report

Use of genomic data in risk assessment

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A report on the Contemporary Concepts in Toxicology workshop 'Use of Genomic Data in Risk Assessment: State of the Art 2001' held by the Society of Toxicology, Washington DC, USA, 7-8 November 2001.

"In the 21st century, the new genomic technologies will greatly improve the accuracy of risk assessment, allowing identification of sensitive subpopulations and, ultimately, allow personalized risk profiling for each individual based on their genetic composition". So declared the announcement for the Contemporary Concepts in Toxicology meeting, a workshop designed to examine the genomic technologies that might be applied to such risk assessment and their implications for risk characterization and understanding of gene interactions. Three significant areas of risk assessment were considered: the risk from inadvertent exposure to environmental toxicants; the risk of adverse response to prescribed pharmaceuticals; and the risk of developing disease because of genetic predisposition.

John Weinstein (National Cancer Institute, Bethesda, USA) emphasized in the plenary talk that there has to be a synergy between the new '-omic' research and traditional hypothesis-driven science, and that there are now a number of useful genomic technologies, including comparative genomic hybridization, single-nucleotide polymorphism (SNP) analysis, restriction landmark genome scanning, and spectral karyotyping. 'Transcriptomics' is the current dominant force in genomics, however, and Edwin Clark (Millennium Pharmaceuticals, Cambridge, USA) reported the use of differential expression analysis to elucidate markers that indicate whether a patient has an increased risk of developing ovarian cancer. Transcript profiling was used in drug-discovery studies to identify possible drug targets, and in efficacy studies to identify biomarkers that allow prediction of a patient's response to chemotherapy. No further details about the markers or the drug targets analyzed were presented. Clark also described how pharmacogenomics tests carried out *ex vivo* on cancer biopsies could help to identify responders and non-responders to drug treatment, as defined by the expression of selected genetic biomarkers, allowing the use of alternative therapies if a patient is found to be a probable non- or adverse responder to the standard drug.

SNP analysis is an important component of the arsenal of genomic techniques, and Arthur Holden (First Genetic Trust Inc., North Deerfield, USA) described how The SNP Consortium (TSC) [http://snp.cshl.org] was established through the collaboration of multiple organizations to advance the field of medicine and aid the development of genetics-based diagnostics and therapeutics. SNPs are the most widespread and stable form of genetic variation, are easy to detect and can be stored as digital code. TSC has so far identified 1.7 million SNPs, 1.4 million of which are described as 'unencumbered' - that is, they have no intellectual property rights attached. Doug Bell (National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, USA) presented some well-characterized examples of genetic polymorphisms modifying exposure-related responses; for example, heterozygote carriers of the mutation that causes sickle cell anemia show reduced susceptibility to malaria, a polymorphism in the cytochrome 450 form CYP2D6 affects adverse drug responses, and alcohol intolerance is influenced by polymorphisms in aldehyde dehydrogenase. Bell warned, however, that determining a quantitative measure of exposure is difficult in humans, so combining this with genetic information to assess risk is quite problematic. There is thus a need to determine functional relationships between genotype and phenotype, remembering that simple polymorphisms may have different effects depending on the chemical and the target organs that are considered.

It appears likely that genomic data will find, and possibly even require, some support from proteomic studies. When

examining the correlation coefficients for mRNA and protein expression in human gliomas and lung cancer, Sam Hanash (University of Michigan, Ann Arbor, USA) found that mRNA and protein expression levels showed good correlation for some genes, while they did not for others, and in some cases they were even negatively correlated (perhaps as a result of negative feedback). Hanash thus proposed that evaluating the cellular response to a toxic challenge should not necessarily be based on changes in gene expression *per se*, but on how the expression relationship changes between a specific mRNA and the corresponding protein.

Harvey Mohrenweiser (Lawrence Livermore National Laboratory, Livermore, USA) has been considering the genetic mechanisms underlying cancer susceptibility, in particular the roles of DNA-repair genes. He reasoned that it is not the amount of DNA damage a cell sustains *per se* that produces a cancerous phenotype, but the amount of damage present at the time of cell division. He referred to a published study (Wu *et al.*, *Cancer* 1998, **83:**1118-1127), which reported that sensitivity of cells to benzo[a]pyrene diol epoxide (BPDE, a metabolic product of benzo[a]pyrene, a constituent of tobacco smoke) was significantly associated with lung carcinoma, and suggested that variation in BPDE sensitivity might be due to different repair or sensitivity pathways. Mohrenweiser is thus currently assessing whether genotypes associated with reduced repair capacity can be used as biomarkers of increased cancer risk. A similar view was conveyed by Jim MacGregor (Food and Drug Administration (FDA), Rockville, USA) when he suggested that elucidation of the molecular systems that protect and repair cell function will provide a new generation of surrogate biomarkers for monitoring cell damage. MacGregor was, however, reluctant to predict when the FDA would be in a position to accept data from new genomic methods as support for applications for FDA approval. He said this would occur "when it's appropriate", namely, when there is consensus within the scientific community and the responsible FDA center about the suitability of any given approach. MacGregor anticipated that no single genomic technology will meet all assessment needs, but that different methods will predominate under different circumstances. He also predicted that risk assessment will embrace an increasingly multidisciplinary approach requiring the integration of pharmacology, toxicology, pharmacokinetics and other disciplines.

While many of the speakers discussed the application of genomics to the clinic, for example, by identifying the possibility of adverse drug reactions and determining genetic predisposition to disease development, Bill Farland (US Environmental Protection Agency (EPA), Washington DC, USA) provided an overview of how genomics might aid the risk assessment process for environmental exposure. Such exposures occur through air, water and food, and are often inadvertant, unknown or inescapable. Genomics, he predicted, will be particularly useful in identifying and demonstrating the mode of action of any toxic effects through highlighting the gene-expression networks and/or pathways that are affected. Such information will also help identify and measure key events (for example, changes following receptor-ligand interaction or changes in DNA and chromosomes, such as DNA strand breaks or base modifications induced by environmental toxicants) that are useful in risk assessment. Genomics will also help our understanding of whether toxicology data generated from animal models are relevant to human health. George Gray (Harvard Center for Risk Analysis, Boston, USA) added that although genomic information has real potential to improve risk prediction, changes in genotype or phenotype *per se* may not be relevant to risk, and variability between individuals in exposure and sensitivity must be incorporated into the risk analysis process. For example, some individuals smoke 40 cigarettes a day all their life without developing lung cancer, whereas others who smoke much less may develop cancer at a relatively early age. Many smokers show characteristic genetic or phenotypic changes in their lung epithelia that are generally indicative of increased risk of progressing to a disease state. For some individuals, however, these changes do not represent a significantly increased risk as certain genetic makeups and/or life style and environmental factors (notably diet) may strongly reduce the possibility of further disease progression. He also made a plea for greater interaction between toxicologists and regulators, as the latter often rely on the former to identify specific risk indicators.

Dale Hattis (Clark University, Worcester, USA) suggested that genomic analysis may be less relevant for risk assessment than measuring functional phenotypes such as enzyme activitation or deactivation and DNA-repair function. Like many other speakers, he expressed the view that gene-expression profiling holds promise, but a good deal of work is still needed, and it may be as long as ten years before such data can be usefully incorporated into risk assessment for environmental exposures. Many participants at the meeting hoped that this will turn out to be a conservative estimate, and Ray Tennant (NIEHS, Research Triangle Park, USA) provided some hope for this when he reported how researchers at NIEHS have already successfully classified mRNA expression profiles in animals exposed to certain chemicals.

The use of genomic data in risk assessment also faces obstacles in the form of the complex social, moral and legal issues relating to the protection of human subjects, the privacy of genetic information and the possibility of discriminatory use of such data. The ethical, legal and social implications (ELSI) program, spawned from the human genome project (HGP), demonstrates the seriousness with which scientists and policy makers are treating public skepticism over the control of powerful genomic technologies. As Richard Sharp (NIEHS, Research Triangle Park, USA) pointed out, however, ELSI is funded in large part by the HGP budget and there has been justifiable concern that the bioethicists

may not be as independent as they should be. The main critique is that they have failed to properly address controversial issues, such as the cloning of embryos, and their testimony may inhibit the pace of science. Sharp concluded that the scientific community should be mindful that although the services of bioethicists may currently be viewed as a commodity, their involvement in research is nevertheless likely to increase and should be viewed as a mutually beneficial arrangement that can facilitate identification of ethical issues that would otherwise go unnoticed.

There was general consensus that genomic techniques must be improved so they can return more sensitive, reproducible and quantitative data before they can realistically be used in the risk-assessment process. There is also a need to standardize and validate the protocols that are developed, and maintain rigorous quality control. The good news is that we can anticipate such technical issues to be overcome in relatively short course. Of more concern is how to interpret the vast quantities of complex genomic data. Without a clear understanding of, for example, gene-environment interactions, differences between species and individual responses, and the qualitative and quantitative linkages between toxicity and disease, there is real potential for disagreement or misinterpretation of data where risk assessment is concerned. Nevertheless, the field of genomics (and proteomics) is developing fast; there will be many opportunities for applying genomics and proteomics to risk assessment and these need to be recognized and acted upon by regulatory agencies such as the EPA and FDA. Developing genomic (and proteomic) applications will require significant investment in both basic and applied research, and the impact on regulatory practices will make an agreement on certain policies necessary.

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