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Workshop 2.1
Toxicogenomics: Impact on human health*

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Abstract: Toxicology is the science of adverse effects of chemicals, drugs, environmental agents, and stressors. Genomics defines the structure, sequence (code), and function of the entire DNA complement of organisms. The interface of these diverse disciplines is called toxicogenomics and is based upon the application of genomic technologies to define globally the changes in gene expression (both mRNA and proteins) as a consequence of exposures. DNA microarray technology enables the simultaneous measurement of transcription of thousands of genes using microchips containing thousands of probes of complementary DNA (cDNA) immobilized in a predetermined array. The ultimate application of this technology to toxicology holds great promise but faces several formidable problems. With the solution to these problems, it will be possible to develop a substantial database of Chemical Effects in Biological Systems (CEBS). Such a database will provide the capacity to relate specific changes in gene expression to specific adverse effects and to look for similar pathways in different organisms. Such data will provide an objective way of assessing surrogate systems for reporting or predicting potential adverse effects in humans. While the potential for toxicogenomics is thus very high for studying active substances, the task must be approached in a deliberate, incremental manner to insure that only high-quality data are compiled and analyzed. This workshop will present the latest results of research conducted in leading international laboratories studying endocrine-mediated toxicity.

Toxicogenomics can be described as a new approach to understanding the genetic mechanisms and biochemical pathways to disease by environmental toxicants via the simultaneous analysis of gene and protein expression. For the first time, by careful comparison of perturbations between normal and diseased metabolic pathways and variance in expressed genes, investigators can decipher the complete mechanism of how and where toxicants disrupt normal processes that lead to disease. Over the last decade, the genomic revolution has been fueled by the meteoric rise in analytical technology, and the science of toxicogenomics represents a logical extension of the knowledge gained from the fields of gene and protein discovery. Publication of the human genome sequence draft five years earlier than anticipated was greatly dependent on the increased rate of sequence acquisition made possible by high-throughput technology and more sophisticated algorithms for gene discovery and identification.

Toxicologists and environmental health scientists have studied the effects of the environment on human health for many years. Adverse environmental effects have been identified, and important progress has been made in mitigating exposure to harmful agents such as X-radiation, UV-light, lead, pesticides, and dioxins. Toxicological research has attempted to develop an efficient, cost-effective, and comprehensive strategy for predicting and preventing toxic responses in humans. However, progress to-

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ward this goal has been proportionate to the existing technologies and level of scientific knowledge. The field of toxicology could not have risen to this current challenge by using only the less efficient technologies of the past several decades.

The genomic knowledge and technological developments surrounding the human genome program have yielded a great legacy to toxicogenomic research because the road to understanding the genetic and biochemical pathways to disease from environmental toxicants has been significantly widened by this wealth of genetic information. Furthermore, the accelerated discovery of genetic knowledge of both human and nonhuman genomes has empowered toxicology to reach beyond its classical boundaries of pathology and clinical chemistry to include all the genes and proteins in the biochemical pathways toward the manifestation of disease. Thousands of genes and proteins can now be analyzed simultaneously; it is now possible and practical to carefully map the effects of a toxic chemical as a function of dose and time against perturbations in networks of expressed genes and proteins. In the next decade, the culmination of all these measurements will begin to elucidate all the gene and protein modulations in an organ, tissue, or cell as it proceeds through its defense against the toxicant to reach recovery or toward a disease outcome or cell death.

The National Institute of Environmental Health Sciences is uniquely positioned with the National Center for Toxicogenomics (NCT) to provide leadership for the development of a unified strategy for toxicogenomics studies and a public knowledge base with the informatics infrastructure to allow scientists worldwide to share equally in its benefits and products. By providing a focus for technological coordination and basic research, a centralized public knowledge base and a center for coordination among all the partners in academia and the pharmaceutical and chemical industries, the NCT will facilitate this diverse national effort. The NCT seeks to achieve not only economies of time, cost, and effort, but also contributions to the successful development of a broad scientific consensus on the toxicogenomic applications to the improvement of human health.

The NCT has established five goals for its toxicogenomics program: (1) facilitate further development of gene expression and proteomic methodology; (2) create a public database relating environmental stressors to biological responses; (3) collect information relating environmental exposures to disease; (4) develop an improved paradigm for use of computational mathematics for understanding responses to environmental stressors; and (5) identify biomarkers of disease or exposure to enhance environmental health. It is important to realize that accomplishing these goals is a long-term effort and that the magnitude of this task is far greater than the physical resources and intellectual capacity of any individual institution. Therefore, the NCT is being established as a unique fusion of intramural laboratories, extramural grants, cooperative research agreements, and resource contracts.

Although the field of toxicogenomics is in its early stages and will be a long-term effort, it is already clear that the benefits of this methodical and comprehensive approach will be both extensive and exciting. The breath and scope of knowledge derived from this effort will be used to understand the underlying mechanism of disease by toxic chemicals, as well as for drug discovery, and also will be a critical platform for developing interventional and remedial strategies to interrupt the disease process.

The program presented at the SCOPE/IUPAC conference clearly showed a portion of the spectrum of research that will be embraced by the field of toxicogenomics. The following extended abstracts cover the presentations at the conference in greater detail to allow the reader a more complete appreciation for the excitement toxicogenomics is generating throughout the research community.