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Exploring Human Genomic Plasticity and Environmental Stressors: Emerging Evidence on Telomeres, Copy Number Variation, and Transposons
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SPEAKERS/MODERATORS/PANELISTS BIOSKETCHES

John M. Balbus, M.D., M.P.H., serves as a senior advisor to the Director on public health issues and as NIEHS liaison to its external constituencies, stakeholders, and advocacy groups. He also leads NIEHS efforts on climate change and human health. In this capacity he serves as HHS principal to the U.S. Global Change Research Program, for which he also co-chairs the Interagency Cross-Cutting Group on Climate Change and Human Health. Dr. Balbus' background combines training and experience in clinical medicine with expertise in epidemiology, toxicology, and risk sciences. He has authored studies and lectures on global climate change and health, transportation-related air pollution, the toxic effects of chemicals, and regulatory approaches to protecting susceptible subpopulations. Before joining the NIEHS, Dr. Balbus was Chief Health Scientist for the non-governmental organization Environmental Defense Fund. He served on the faculty of The George Washington University, where he was founding Director of the Center for Risk Science and Public Health, founding co-Director of the Mid-Atlantic Center for Children's Health and the Environment, and Acting Chairman of the Department of Environmental and Occupational Health. He maintains an adjunct faculty appointment at the Johns Hopkins Bloomberg School of Public Health. Dr. Balbus received his A.B. degree in Biochemistry from Harvard University, his M.D. from the University of Pennsylvania, and his M.P.H. from the Johns Hopkins School of Public Health. In addition to current membership on the Institute of Medicine Roundtable on Environmental Health Sciences, Research and Medicine, Dr. Balbus has also served as a member of the EPA Science Advisory Board, the National Research Council's Board on Environmental Studies and Toxicology and the EPA Children's Health Protection Advisory Committee. He is a member of the American College of Physicians, the American Public Health Association, and the Society of Toxicology.

Laurence H. Baker, D.O., has been engaged in clinical trials research all of his career. He is trained in internal medicine, medical oncology and pharmacology. Dr. Baker has chaired SWOG for the past 7 years. SWOG is one of 4 NCI funded cancer clinical trial organizations for adult patients engaged in studies to prevent, control or treat cancer and has continuous NIH funding for 55 years. SWOG has nearly 500 sites participating in studies and includes 24 of our nations NCI designated cancer centers. In the past 5 years nearly 30,000 participants were enrolled in the 168 controlled prospective clinical trials resulting in approximately 600 published manuscripts. SWOG has an active biobank of participant specimens including: cancer tissues, whole blood, serum, nucelotides and toe nail clippings totaling more than 1, 000,00 specimens that can be correlated with clinical outcome of our trials. The bank is located at Nationwide Childrens Hospital in Columbus. Prof Tlsty is a member of our genomics task force that provides scientific oversight. Dr. Baker grew up in Brooklyn New York and has maintained his Brooklyn "attitude" despite living in the Midwest since 1962. He is a graduate of Brooklyn College, and University of Osteopathic Medicine in Des Moines Iowa. His medical fellowship was at Wayne State University. He rose the ranks at Wayne State and was the heme/onc division chief and then cancer center director. He served as interim chair of Medicine. He was recruited to the University of Michigan in 1994 and has been the Director of Clinical Programs and Deputy Director of the Cancer center before becoming chair of SWOG. He has been named as the first collegiate professor of oncology at Michigan and maintains keen interest in clinical trial design and sarcoma biology.

Maria A. Blasco, Ph.D.**,** obtained her PhD from *Universidad Autónoma de Madrid* (Madrid, Spain) in 1993. That same year, she joined the Carol W. Greider's lab at Cold Spring Harbor Laboratory (New York, USA). In 1997 she returned to Spain to start her own research group and she joined the CNIO in 2003 as Director of the Molecular Oncology Programme and Leader of the Telomeres and Telomerase Group. She and was appointed CNIO Director in 2011.

George P. Daston, Ph.D., has been employed at Procter & Gamble Company since 1985, where he is Victor Mills Society Research Fellow. Dr. Daston has spent his entire career in research to understand the effects of exogenous chemicals on biological systems, especially the developing embryo, fetus and child. His research interests include teratogenic mechanisms, in vitro methodologies, and risk assessment. He has published over 100 peer-reviewed articles, reviews and book chapters, and has edited three books. Dr. Daston's professional activities include serving as Councilor of the Society of Toxicology (2001-03); President (1999-2000) of the Teratology Society; member of the National Academy of Sciences Board on Environmental Studies and Toxicology (1995-98); member of the EPA Board of Scientific Counselors (2002-08); member of the U.S. National Toxicology Program Board of Scientific Counselors (2003-06, Chair in 2006); member of the National Children's Study Advisory Committee (2003-06); and member of EPA's Endocrine Disrupter Screening and Testing Advisory Committee (EDSTAC). He has served on several NRC committees, including the Committee on Developmental Toxicology, Committee on Research Opportunities and Priorities for EPA, and the Subcommittee on Arsenic in Drinking Water. Dr. Daston has served on the organizing committees for numerous government and private sector-organized workshops on reproductive toxicity, risk assessment, and non-animal alternatives. He chaired NIEHS/ICCVAM working groups evaluating the state of validation of the Frog Embryo Teratogenesis Assay - Xenopus (FETAX) assay for teratogen screening and receptor binding and transcriptional activation assays for estrogens and androgens. Dr. Daston is Editor-in-Chief of Birth Defects Research: Developmental and Reproductive Toxicology. Dr. Daston is an Adjunct Professor in the Department of Pediatrics and Developmental Biology Program at the University of Cincinnati and Children's Hospital Research Foundation. Dr. Daston received his Ph.D. from the University of Miami and post-doctoral training at the U.S. EPA's laboratories in Research Triangle Park, North Carolina.

Elissa Epel, Ph.D., is a health psychologist focusing on stress pathways toward biological aging. For the past 15 years, she has studied stress in the lab and in the field, using naturalistic stressors, and associations with an early aging syndrome. She examines how stress processes lead to early disease precursors, focusing on overeating, abdominal obesity, and immune cell aging (the telomere/telomerase maintenance system). She has found that people's propensity to be stress reactive, psychologically or in terms of cortisol reactivity, is associated with overeating, abdominal obesity, and accelerated cell aging. With UCSF colleagues Elizabeth Blackburn and Jue Lin, she found that stress perceptions and stress arousal are related to telomere shortness and dampened telomerase activity. Their group now collaborates with many other labs extending this work from animal models to population studies. Their collaborative teams are examining how stress reduction interventions affect functioning of the telomere/telomerase maintenance system. Epel and colleagues also have an ongoing intervention to alter stress and overeating in low income pregnant women, to examine effects on offspring. Epel studied psychology and psychobiology at Stanford University (BA, 1990), and clinical and health psychology at Yale University (PhD, 1998). She completed an NIMH funded postdoctoral fellowship at UCSF, where she has stayed on as faculty, in the Department of Psychiatry. Epel has received awards from the American Psychological Association, for her research conducted as a student (1996, 1998), a junior investigator (2005), and more recently, the Early Career Award (2008). She also was awarded the Academy of Behavioral Medicine Research Neal Miller Young Investigator Award, and the International Society for Psychoneuroendocrinology's Young Investigator Award.

Jennifer L. Freeman, Ph.D., is an Assistant Professor in the School of Health Sciences at Purdue University in West Lafayette, Indiana. Dr. Freeman’s research interests are in molecular and environmental toxicology, cytogenetics, genomics, and epigenomics. Current research efforts in the Freeman laboratory are focused on investigating the adverse health effects of exposure to environmental stressors on human and environmental health using the zebrafish model system. Dr. Freeman was involved in the cytogenetic mapping of the zebrafish genome in efforts to establish an accurate and comprehensive genome sequence. She also developed the first array comparative genomic hybridization platforms for the zebrafish that were applied to investigate genomic imbalances in zebrafish developmental mutant and disease models including numerous cancer models. In addition, these platforms were applied to define and characterize copy number variants (CNVs) in the zebrafish genome. Ongoing research projects in the Freeman laboratory are defining the underlying genetic and epigenetic mechanisms of toxicity of environmental stressors with current focus on pesticides, metals, and radiation. These projects are identifying genetic biomarkers and molecular pathways of the immediate adverse

impacts of a developmental exposure, the lasting impacts of this developmental exposure throughout the lifespan, and the analysis of subsequent generations linking genetic, epigenetic, and phenotypic assessments. These studies are investigating a developmental origin of adult disease pathogenesis with a specific focus on neurodegenerative disorders, cancer, and reproductive alterations. Dr. Freeman received her Ph.D. in Molecular Cytogenetics and Environmental Toxicology from the University of Illinois in Champaign-Urbana, Illinois and completed her post-doctoral training at Harvard Medical School and Brigham and Women's Hospital, Boston, Massachusetts.

David P. Gilley, Ph.D., received his PhD from Indiana University, Bloomington and was an ACS postdoctoral fellow with the eminent telomere biologist Dr. Elizabeth H. Blackburn at the University of California, San Francisco. After his postdoctoral training, he was a Scientist at Lawrence Berkeley National Laboratory and then joined the faculty at the Indiana University School of Medicine. Dr. Gilley's current research at the IUSM focuses on two study areas: *1)* exploring the hypothesis that telomere dysfunction is a key cause of genomic instability in cancer, and *2)* identifying the nature of mammalian telomere maintenance and telomerase activation in human breast repopulating cells and how these processes are altered during tumorigenesis. His laboratory is developing innovative technologies to detect and analyze telomere fusions from tumor tissue and circulating tumor cells/DNA. Dr. Gilley's laboratory has made substantial progress in the detection and analysis of telomere dysfunction in human cancers and, in the analysis of normal and tumor stem and progenitor cells from the human breast. The clinical goals of his research are to develop genetic-based telomere dysfunction markers for early cancer detection and monitoring disease recurrence.

Thomas W. Glover, Ph.D., is Professor in the Departments of Human Genetics and Pediatrics at the University of Michigan Medical School. Dr. Glover's broad research interests include the mechanisms of genome instability and the identification and function of genes involved in human genetic disorders, with over 130 peer-reviewed publications in these areas.His research on CNVs centers on the mechanisms involved in their formation and the identification of both genetic and environmental risk factors. His laboratory determined that replication stress induces a high frequency of CNVs in cultured human cells and they have developed a model system to identify the factors involved in this process, including DNA repair genes and potential CNV mutagens. Among their findings is that low-dose hydroxyurea treatment, equivalent to human therapeutic exposures, is a potent inducer of CNVs. Current work includes testing the replication stress hypothesis for CNV mutagenesis directly *in vivo* in the germline and somatic cells of HU-treated mice. Dr. Glover earned his Ph.D. degree in Genetics in 1979 from Michigan State University.

Randal Johnston, Ph.D., received a BSc degree (1975) from the University of Victoria and his PhD (1980) and postdoctoral training from Stanford University in California and has been a faculty member of the University of Calgary since 1984. He was appointed for 10 years as the Terry Fox Professor for Cancer Research and then as the Associate Vice-President (Research) and subsequently as President of Genome Prairie/Alberta (a not-for-profit corporation dedicated to genomics research as part of the Genome Canada program), before returning full-time in 2006 to his academic position in the Department of Biochemistry and Molecular Biology and his new roles as General Secretary for the Canadian Society for Molecular Biosciences and Co-Director of the Alberta Cancer Research Tumour Bank and Biorepository. Dr. Johnston's research focuses on cancer genomics and novel viral therapies for cancer that show great promise and are currently being used in clinical trials.

James R. Lupski, M.D., Ph.D., D.Sc.,is Cullen Professor and Vice Chair of Molecular and Human Genetics. Dr. Lupski received his initial scientific training at the Cold Spring Harbor Laboratory as an Undergraduate Research Participant (URP) and at New York University receiving his undergraduate degree in chemistry and biology (1979) and completing the M.D./Ph.D. program in 1985. In 1986 he moved to Houston, Texas for clinical training in pediatrics (1986-1989) and medical genetics (1989-1992) and then established his own laboratory at Baylor College of Medicine where he remains, and as of 1995, as the Cullen Professor of Molecular and Human Genetics and Professor of Pediatrics. Through studies of Charcot-Marie-Tooth peripheral neuropathy, a common autosomal dominant trait due to a submicroscopic 1.5 Mb duplication, and Smith-Magenis syndrome, a contiguous gene deletion syndrome, his laboratory has delineated the concept of 'genomic disorders' and established the critical role of copy number variation (CNV) and gene dosage in conveying human disease phenotypes. An increasing

number of human diseases are recognized to result from recurrent DNA rearrangements (recent examples include obesity and both autism and schizophrenia) involving unstable genomic regions and have thus been classified as genomic disorders. The conceptualization and mechanistic understanding of genomic disorders has been among the lab's most significant contribution. Dr. Lupski's laboratory has also used chromosome engineering to develop mouse models for genomic disorders. Recently, the laboratory's CMT studies in collaborations with Richard Gibbs and the Baylor Human Genome Sequencing Center resulted in the first personal genome sequence to identify a "disease gene" by whole genome sequencing (WGS) and demonstrated the utility of WGS for optimizing patient management. These latter investigations further elucidated the potential role of rare variants in complex traits such as carpal tunnel syndrome and fibromyalgia. For his work in human genomics and the elucidation of genomic disorders Dr. Lupski was awarded a Doctor of Science degree honoris causa in 2011 from the Watson School of Biological Science at the Cold Spring Harbor Laboratory. He has coauthored over 540 scientific publications, is a co-inventor on more than 20 patents regarding molecular diagnostics and has delivered over 430 invited lectures in 35 countries.

John V. Moran, Ph.D., John V. Moran received his Ph.D. in Biochemistry from the University of Texas Southwestern Medical Center in 1994. After postdoctoral work with Dr. Haig Kazazian at the Johns Hopkins Medical Institute and the University of Pennsylvania Medical School, he joined the faculty at the University of Michigan Medical School in 1998. He was promoted to the rank of Associate Professor in the Departments of Human Genetics (with tenure) and Internal Medicine (without tenure) in 2003. He then was appointed as an Investigator of the Howard Hughes Medical Institute in August 2008, and to Full Professor of Human Genetics (with tenure) and Internal Medicine (without tenure) in September 2008. He subsequently was appointed the Gilbert S. Omenn Collegiate Professor of Human Genetics in June 2010. Dr. Moran's research focuses on a class of 'jumping genes' (*i.e.*, retrotransposons) known as LINE-1 sequences. LINE-1 sequences comprise approximately 17% of human genomic DNA. The overwhelming majority of LINE-1 sequences have been rendered inactive by mutation. However, it is estimated that the average human genome harbors approximately 80-100 actively mobile LINE-1 elements. LINE-1 mobility (*i.e.*, retrotransposition) in both germ line and somatic cells can lead to sporadic cases of human disease. Dr. Moran's laboratory uses inter-disciplinary genetic, molecular biological, biochemical, genomics, and computational approaches to determine the following: the molecular mechanism of LINE-1 retrotransposition; the impact of LINE-1 retrotransposition on human genome evolution; and the influence of host proteins on LINE-1 retrotransposition. Dr. Moran has worked in the transposable element field for approximately 20 years and has published over 50 articles in this area of research.

Kenneth Ramos, M.D., Ph.D., is Distinguished University Professor of Biochemistry and Molecular Biology and Director of the Center for Environmental Genomics and Integrative Biology. He is a leading expert in the study of gene-environment interactions and personalized and genomic medicine. A major focus in his laboratory is the elucidation of molecular mechanisms of reactivation of mammalian retroelements and their role in reprogramming the human genome. Dr. Ramos completed a B.S. in Pharmaceutical Sciences and Chemistry (Magna Cum Laude) at the University of Puerto Rico, a Ph.D. in Biochemical Pharmacology at the University of Texas at Austin, and an M.D. degree with postgraduate preliminary training in Internal Medicine at the University of Louisville Health Sciences Center. He has held faculty positions at the University of the Sciences in Philadelphia, Texas Tech University Health Sciences Center, Texas A&M University and the University of Louisville School of Medicine. He is currently affiliated with the Center for Environmental Genomics and Integrative Biology, James Graham Brown Cancer Center, Center for Genetics and Molecular Medicine, Birth Defects Center, Gheens Center for Aging, and Center for Environmental and Regulatory Metabolomics. Dr. Ramos is recipient of the Society of Toxicology Achievement Award, Astra Zeneca Traveling Lectureship Award and Distinguished Service Award from the American Heart Association. He was named Associate of the National Academy of Sciences and Fellow of the Academy of Toxicological Sciences.

Dale P. Sandler, Ph.D., is Chief of the Epidemiology Branch in the Division of Intramural Research at the National Institute of Environmental Health Sciences (NIEHS), NIH, and head of the Chronic Disease Epidemiology Group. She is adjunct professor of Epidemiology at the University of North Carolina at Chapel Hill, past editor of the journals, *Epidemiology,* and the *American Journal of Epidemiology,* and a

past president of the American College of Epidemiology. Dr. Sandler has published more than 250 scientific articles, reviews and commentaries. She received an M.P.H. from Yale University in 1975 and a Ph.D. in Epidemiology from The Johns Hopkins University in 1979. Dr. Sandler's research focuses on a wide range of chronic diseases and conditions, including risk factors for chronic kidney disease, leukemia, lung cancer, and breast cancer. She studies the role of early life and reproductive factors in risk for diseases later in life as well as potential health effects of radon and agricultural exposures. In 1993, Dr. Sandler partnered with investigators from the National Cancer Institute and the Environmental Protection Agency to develop the **Agricultural Health Study**, an ongoing prospective study of the health of licensed pesticide applicators and their spouses. She is Principal Investigator of **The Sister Study**, a prospective study of more than 50,000 sisters of women who have had breast cancer designed to identify environmental and genetic causes of breast cancer and other conditions. The study will also evaluate factors that affect prognosis for women diagnosed with breast cancer. A related study, **The Two Sister Study**, uses a family design to explore genetic and environmental risk factors for early onset breast cancer. Dr. Sandler is Principal Investigator of the recently initiated long-term follow-up study of the health of Gulf of Mexico Deepwater Horizon oil spill clean-up workers. This study, known as the **GuLF STUDY**, is recruiting as many as 40,000 workers from across the US and conducting clinical baseline examinations of about 15,000 of those workers who currently reside in Gulf States. A related study is measuring exposure to petroleum-related chemicals in Gulf area communities to identify sources of exposure and factors associated with elevated exposure levels.

Daniel Shaughnessy, Ph.D., is a Program Administrator at the National Institute of Environmental Health Sciences in the Susceptibility and Population Health Branch in the Division of Extramural Research and Training. He manages a portfolio of grants related to DNA Repair and Mutagenesis. He also oversees grants on the development and validation of biomarkers of response to environmental stress, a program initiated in the Genes, Environment and Health Initiative, Exposure Biology Program. Dan is the program contact for the small business programs (SBIR/STTR) at NIEHS. As a postdoctoral fellow in the Laboratory of Molecular Carcinogenesis at NIEHS, he conducted research on the risk and protective effects of dietary factors on DNA damage in humans. He received a PhD from the University of North Carolina at Chapel Hill in 2002 and an MSPH degree from UNC in 2000, studying the molecular mechanisms of dietary antimutagens.

Joseph R. Shaw, Ph.D., earned his doctoral degree from the Center for Toxicology at the University of Kentucky in 2001. He received post-doctoral training at Dartmouth College working to bridge studies of genes and their relationship to toxicologically relevant phenotypes with those that describe the effects environmental pollution on populations. He joined the faculty of the School of Public and Environmental Affairs at Indiana University, Bloomington in 2007. His research group seeks to discover critical, specific and causative molecular toxicological and disease pathways resulting from complex environmental exposures. They embrace new high-throughput molecular techniques and couple these with evolutionary theory, statistical analysis and bioinformatics in order to integrate toxic-response across levels of biological organization. Current projects *(i)* dissect variation in disease and toxicant response within and between populations; *(ii)* identify the evolutionary mechanisms and partition of the costs of physiological acclimation and long---term population level adaptation to chemical stress, especially metals, *(iii)* elucidate the molecular underpinnings of evolved metal tolerance, and *(iv)* understand the causes and phenotypic consequences of gene copy number variation in metal stressed populations.

Thea D. Tlsty, Ph.D., is a Professor in the Department of Pathology, Director of the Program in Cell Cycling and Signaling in the UCSF Comprehensive Cancer Center and Director of the Center for Translational Research in the Molecular Genetics of Cancer at the University of California, San Francisco, School of Medicine, San Francisco, CA. She received a Ph.D. in Molecular Biology from Washington University. Dr. Tlsty trained with Dr. Robert Schimke at Stanford University as a Postdoctoral Fellow and Senior Research Associate in the Department of Biological Sciences before she was recruited to the University of North Carolina as Assistant Professor of Pathology and Member of the UNC Lineberger Comprehensive Cancer Center. In 1994 she joined the faculty at UCSF where she is currently a Professor of Pathology. She also serves as an Avon Scholar and a Komen Scholar for each Foundation studying breast cancer research. Dr. Tlsty studies genetic, epigenetic and functional changes involved in

the earliest steps of epithelial cancers and how interactions between stromal components and epithelial cells collaborate to moderate carcinogenesis. Her research studies of human epithelial cells from healthy individuals are providing novel insights into how early molecular events affect genomic integrity and fuel carcinogenesis, tumor heterogeneity and malignant evolution. Prior work from her laboratory has shown that surrounding stroma can dramatically influence tumorigenesis both through signaling pathways and epigenetic reprogramming. She investigates how these changes are initiated and moderated, as well as their consequences for clinical disease. These insights are applied in risk assessment, early detection, and prognostic studies. For example, her studies have allowed the development of a clinical assay that can predict which pre-malignant lesions will cause cancer even ten years before the cancer forms. This assay is urgently needed to prevent over treatment of pre-cancers and allow targeting of aggressive measures to those that will form metastatic lesions. Areas of particular interest include human breast carcinogenesis and the role of tumor suppressor genes in regulating premalignant phenotypes and lineage plasticity. Her studies use molecular, biochemical and cellular analyses to evaluate primary human cells, develop recombinant models of cell-cell societal interactions and apply novel information to intact human tissue for clinical use.

Cheryl Lyn Walker, Ph.D., is Director of Texas A&M Health Science Center (TAMHSC) Institute of Biosciences and Technology in Houston and Welch Chair in Chemistry and a joint position as Clinical Professor in the College of Veterinary Medicine & Biomedical Sciences at Texas A&M University. Previously, Dr. Walker was Ruth and Walter Sterling Professor of Carcinogenesis at The University of Texas M.D. Anderson Cancer Center. She earned a Ph.D. in cell biology from Southwestern Medical School. Dr. Walker's research interests include studying the genetic basis of susceptibility to cancer, specifically examining the interaction of carcinogens with genes during tumor development, characterizing the effects of endocrine disruptors on human health, and developing animal models for human disease. She also studies the molecular mechanisms of kidney, breast and uterine cancers and the effect of hormones of gene expression. She has served on the Board of Scientific Counselors of the National Cancer Institute and the NIEHS National Toxicology Program, and is a past President of the Society of Toxicology.

Helmut Zarbl, Ph.D., is Professor of Environmental and Occupational Medicine at the Robert Wood Johnson Medical School, University of Medicine and Dentistry of New Jersey (UMDNJ). He is a member of the Environmental & Occupational Health Sciences Institute (EOHSI), a joint Institute of UMDNJ and Rutgers, The State University of New Jersey. He is also the Director of the NIEHS Center for Environmental Exposures and Disease at EOHSI, is the Associate Director for Public Health Science at the Cancer Institute of New Jersey. Previously, he was a member of the Divisions of Human Biology and Public Health Sciences at the Fred Hutchinson Cancer Research Center (FHRCR), where he was Director and a Principal Investigator for the NIEHS sponsored FHFRC/University of Washington Toxicogenomics Research Consortium. Dr. Zarbl's research has focused largely on toxicogenomics and functional genomics, carcinogenesis, molecular and cellular biology, and toxicology. Specifically this has included work to understand molecular mechanisms of chemical carcinogenesis, chemoprevntion, and the genetic basis for differential susceptibility to mammary carcinogenesis using both animal and in vitro model systems. Recent studies include the role of circadian rhythm in cancer risk and prevention. His studies in the area of toxicogenomics include the development and application of standards for DNA microarray experiments, and phenotypic anchoring of response of human cells, model organisms (yeast) and target organs (rodents) to toxicants, providing insights into dose and temporal responses, as well as mechanisms of action. Dr. Zarbl is also actively involved in technology development, including his patented work on RNAi and its application to the development of novel platforms for functional genomics (with Engineering Arts, Inc). Dr. Zarbl served on the NRC committee that produced *Application of Toxicogenomic Technologies to Predictive Toxicology and Risk Assessment*. Previously he was an Assistant and Associate Professor at M.I.T. He earned his Ph.D. in Biochemistry from McGill University.