NATIONAL RESEARCH COUNCIL

WORKSHOP ON USE OF EMERGING SCIENCE AND TECHNOLOGIES TO EXPLORE EPIGENETIC MECHANISMS UNDERLYING THE DEVELOPMENTAL BASIS FOR DISEASE

July 30-21, 2009

***Speaker Biographies*[1]**

Max Costa is Professor and Chairman of the Department of Environmental Medicine at the New York University (NYU) School of Medicine. He also is director of the Institute of Environmental Medicine at NYI. His broad research interests are in genetic and epigenetic mechanisms of metal carcinogens. Dr. Costa's research on nickel carcinogensis focuses on histone modification as it relates to nickel-induced gene silencing and the effects of nickel on iron depletion and homeostasis. He is also studying at the interaction and binding of Chromium with DNA and nuclear proteins, as it relates to the development of skin cancer. Dr. Costa's research is currently funded by four grants from the National Institutes of Health. His work on metal-induced carcinogensis is extensively published in peer-review journals. Dr. Costa received his Ph.D. in Pharmacology and Biochemistry from the University of Arizona Medical School, Tuscon, Arizona.

John Greally is an associate professor in the Departments of Genetics and Medicine as well as Faculty Scholar for the Epigenome at Albert Einstein College of Medicine. Dr. Greally's research focuses on the physiology of the epigenome and epigenomic dysregulation in human disease. His epigenomics laboratory investigates bioinformatic characterisation of DNA sequences that distinguish imprinted genes, followed by *in vivo* testing of these candidates. They also have developed a novel assay for genome-wide cytosine methylation studies (the HELP assay), which is being applied to study the epigenomics of cell differentiation, especially male gametogenesis and embryonic stem cell differentiation *in vitro*, and the epigenetic dysregulation that is a major part of neoplastic transformation. The broader question of how epigenomic dysregulation contributes to common complex human genetic disorders is a further interest. Dr. Greally's lab is involved in the initiative to perform a Human Epigenome Project, requiring the combination of high-throughput data generation techniques and the tools with which to analyse the resulting data.

Karl Kelsey is Professor of Community Health and Pathology and Laboratory Medicine at Brown University. Dr. Kelsey is also Director of the Center for Environmental Health and Technology, home to the Brown University Superfund Basic Research Program. Dr. Kelsey research interest is in the application of laboratory-based biomarkers in environmental disease, with experience in chronic disease epidemiology and tumor biology. The goals of his work include a mechanistic understanding of individual susceptibility to exposure-related cancers. In addition, his laboratory is interested in tumor biology, investigating somatic alterations in tumor tissue from patients who have developed exposure-related cancers. This work involves using an epidemiologic approach to characterize epigenetic and genetic alteration of genes in the causal

[1] *Committee and liaison biographies in separate document.*

pathway for malignancy. Dr. Kelsey has contributed to numerous peer-reviewed publications. Dr. Kelsey earned his M.D. from University of Minnesota.

Richard Meehan is the programme leader of Human Genetics Unit at the Medical Research Council in Scotland. Dr. Meehan is also as senior lecturer at the University of Edinburgh and an associate member of the epigenome network of excellence. Dr. Meehan's research focuses on the molecular mechanisms by which the maintenance cytosine DNA methyltransferase, Dnmt1 and MeCPs mediate gene silencing in early embryos and somatic cells. Recently, his laboratory has initiated a joint program (headed by Mike Dixon and David Harrison) that will focus the role of epigenetics and chromatin structure in breast cancer initiation and progression. Prior to joining MRC, Dr. Meehan's research at the Scotland Biochemistry Department in Edinburgh led to the development of *Xenopus laevis* as a model organism to determine the role of DNA methyltransferases (Dnmts) and MeCPs in development. His laboratory made the seminal observation that the maintenance methyltransferase, xDnmt1, is required to maintain transcriptional silencing in pre-mid-blastula transition (MBT) embryos. Dr. Meehan is also part of a consortium (MARCAR) that aims to develop short-term assays to identify non-genotoxic carcinogens (NGCs) and ultimately identify biomarker panels indicative of NGC action, which will underlie new assay systems. Dr. Meehan received his PhD from the MRC Human Genetics Unit in Scotland.

Moshe Szyf is a full professor of pharmacology at McGill Medical School. Dr. Szyf's research is focused on understanding the basic principles of the DNA methylation machinery and its involvement in cancer as well as applying this research towards identifying novel anticancer targets. Dr. Syfs laboratory developed antisense and direct inhibitors of DNA methyltransferase in collaboration with Hybridon Inc. and has demonstrated their efficacy as anticancer agents in preclinical models. His patents and inhibitors of DNA methyltransferase led to the foundation of MethylGene Inc. in Montreal, which is currently testing the antisense inhibitors of DNA methyltransferase in clinical trials (currently at phase II). Dr Szyf's laboratory has also discovered a new and unexpected enzyme and a potential new anticancer target, the demethylase, thus demonstrating that DNA methylation is a reversible biological signal. His lab developed novel inhibitors of this protein that show excellent anticancer and antimetastatic activity in animal models. In collaboration with Dr. Michael Meaney, Szyf's lab discovered an epigenetic mechanism by which maternal behavior results in a stable alteration of the glucocorticoid receptor gene by DNA methylation in the hippocampus of the offspring). New data from his lab shows that a similar process is associated with human suicide and that marks of childhood adversity are found in adult human brains. This data provides a paradigm on how "nurture" alters "nature". Dr. Szyf studied Jewish Philosophy and Political Sciences at Bar Ilan University and obtained his Ph. D. in Biochemistry from the Hebrew University in Jerusalem.

Wan-Yee Tang is a Research Scientist at the University of Cincinnati's College of Medicine in Ohio. Dr. Tang's broad research interest is in epigenetic oncology. Currently, she is investigating the epigenetic effects of xenoestrogens, such as bisphenol A and diethylstilbestrol, on prostate, breast, and uterine cancers. Dr. Tang's research also combines epidemiological studies with epigenetics studies to determine risk factors from that alter the epigenome, and to discover the molecular mechanisms of how environmental factors epigenetically modify the genome. Dr. Tang obtained her B.S. and Ph.D. degrees in Biochemistry at the Chinese University of Hong Kong.

Panelist Biographies

Trevor K. Archer is chief of the Laboratory of Molecular Carcinogenesis and leader of the Chromatin and Gene Expression group at the National Institute of Environmental Health Sciences. Dr. Archer's research interest centers on three major areas of molecular carcinogenesis: evaluating how chromatin remodeling complexes and transcription factors function in transcription from chromatin; analyzing the ubiquitin proteasome system interface with chromatin remodeling, epigenetics and hormone signaling; and exploring how chromatin and epigenetics contribute to human ES cell pluripotency. Prior to joining NIEHS served as a Tenured Associate Professor in the Departments of Biochemistry and Obstetrics and Gynecology at the University of Western Ontario in London Canada. He has published more than 70 peer-reviewed articles in leading biomedical journals as well as several book chapters. Dr. Archer received his PhD in biochemistry from Queen's University, Kingston Ontario Canada

Michele Cleary is Director of the Biology Department of Rosetta Inpharmatics, LLC, a wholly owned subsidiary of Merck & Co., Inc. The primary focus of the group is the development and application of cutting edge genomic approaches including microarray-based gene expression analysis, RNA interference and microRNA technology for the identification and prioritization of novel disease targets and biomarkers. Dr. Cleary underwent postdoctoral training in the field of genomic imprinting at Princeton University as a Life Sciences Research Foundation fellow. In August 2009, she will assume a new role at Merck leading drug discovery efforts within the Merck Research Laboratories Automated Biotechnology group. Dr. Cleary conducted graduate research at Cold Spring Harbor Laboratory and received a Ph.D. in Molecular Genetics from Stony Brook University.

David Dix is a Research Biologist and Acting Deputy Director of the U.S. EPA National Center for Computational Toxicology (NCCT). The goal of the NCCT is to provide the Agency high throughput decision support tools for assessing chemical exposure, hazard and risk. ToxCast is one such tool, testing the utility of computational chemistry, high-throughput screening and toxicogenomics to categorize chemicals and predict toxicity. Dr. Dix is also an adjunct associate professor in the Department of Environmental Science and Engineering at the University of North Carolina at Chapel Hill (UNC Chapel Hill). Dr. Dix received his undergraduate degree in Biological Sciences from the University of Illinois at Chicago, his Ph.D. in Physiology from Rush University in Chicago, and completed his postdoctoral training at the National Institute of Environmental Health Sciences.

Lynn Goldman is a pediatrician, an epidemiologist, and a professor at the Johns Hopkins University Bloomberg School of Public Health, where her areas of focus are environmental health policy, public health practice, and children's environmental health. Dr. Goldman previously served as the assistant administrator for the U.S. Environmental Protection Agency (EPA) Office of Prevention, Pesticides and Toxic Substances (OPPTS). During her tenure at EPA, Dr. Goldman was responsible for the nation's pesticide, toxic substances, and pollution prevention laws, and she was successful in promoting children's health issues and furthering the international agenda for global chemical safety. Prior to joining EPA, Dr. Goldman served in several positions at the California Department of Health Services, including head of the Division of Environmental and Occupational Disease Control. She has served on numerous boards and expert committees,

including the Committee on Environmental Health of the American Academy of Pediatrics and the Centers for Disease Control Lead Poisoning Prevention Advisory Committee. She has also served as a member of numerous National Research Council (NRC) committees, including the Committee on Identifying and Assessing Unintended Effects of Genetically Engineered Foods on Human Health, the Committee on Clinical Trial Registries, and the Committee to Evaluate the Hazardous Materials Management Program of the Bureau of Land Management. She currently is vice chair of the Institute of Medicine (IOM) Roundtable on Environmental Health Sciences, chair of the IOM Committee on Secondhand Smoke Exposure and Acute Cornonary Events, and a member of the NRC Standing Committee on Risk Analysis Issues and Reviews. Dr. Goldman received her MD from the University of California, San Francisco.

L. Earl Gray, Jr is a senior reproductive toxicologist in the Reproductive Toxicology Division, Endocrinology Branch at the U.S. Environmental Protection Agency (US EPA). Dr. Gray is also an Adjunct Professor at the North Carolina State University Department of Toxicology. His research is focused on how individual toxicants and mixtures induce alterations of mammalian reproductive development. Dr. Gray's research team is investigating mechanisms by which chemical exposure alter steroid hormone action during critical developmental periods that result in altered reproductive morphology and function, Mechanisms under investigation include, AR, ER, AhR and hormone synthesis inhibition mediated alterations in the reproductive system. The overall objectives are to compare 1) effects of low doses of toxicants with 2) in vivo tissue levels of the active metabolite(s), 3) determine how mixtures of chemicals with similar and different modes of action interact and to 4) identify in vivo and in vitro mechanisms of action. In their studies, pregnant animals are exposed during developmental stages and the reproductive system of the male and female offspring assessed throughout lactation, puberty, mating and, on occasion, old age. Chemicals of interest include antiandrogenic fungicides, phthalates and xenoestrogens. Currently, they are very interested in how chemicals with divergent mechanisms of action interact during sexual differentiation to determine how often synergistic effects are seen. Dr. Gray has earned 15 USEPA Scientific and Technological Achievement Awards, 2 gold medals for USEPA Service, and 7 bronze medals for USEPA Service. He has contributed to numerous peer-reviewed journal articles and has been an invited lecturer at several national and international symposia. Dr. Gray received his Ph.D. in Zoology from North Carolina State University.

Igor Pogribny is the Senior Research Investigator at the FDA-National Center for Toxicological Research. His research focuses on epigenetic aspects of chemical carcinogenesis, particularly on identification of early biomarkers for early detection of carcinogenic potential of various agents, including diet components. Dr. Pogribny's research effort has resulted in more than 100 peer-reviewed articles. Dr. Pogribny received his Doctoral Degree in Biochemistry and Oncology from Kyiv National University in the Ukraine.

Rebecca Renner is a contributing editor to Environmental Science & Technology Magazine and a contributing correspondent to Environmental Health Perspectives. Her work has also appeared in Science, Scientific American, Salon.com and elsewhere. She holds a M.Sc. from Cornell University and a Ph.D. in geochemistry from Cambridge University.

William Slikker, Jr. is Director of the Food and Drug Administrations (FDAs) National Center for Toxicological Research. Dr. Slikker is responsible for the overall leadership of the FDA's National Center for Toxicological Research that provides innovative and interdisciplinary research to improve public health. Dr. Slikker holds Adjunct Professorships in the Departments of Pediatrics, and Pharmacology and Toxicology at the University of Arkansas for Medical Sciences. He has held leadership positions in several scientific societies including the Teratology

Society, the MidSouth Computational Biology and Bioinformatics Society, the American Society for Pharmacology and Experimental Therapeutics, and the Society of Toxicology. Dr. Slikker has authored or co-authored over 300 publications in the areas of transplacental pharmacokinetics, developmental neurotoxicology, neuroprotection, systems biology, and risk assessment. He is a co-founder of the International Conference on Neuroprotective Agents that has met every other year since 1991. He has served on several national/international advisory panels including those for NIH, HESI/ILSI, EPA, NIEHS, and WHO. Dr. Slikker is also an invited member of The Academy of Toxicological Sciences and Associate Editor for *NeuroToxicology* and *Toxicological Sciences*. Dr. Slikker received his Ph.D. in Pharmacology and Toxicology from the University of California at Davis in 1978.