Workshop on New Approaches for Detecting Environmentally-induced DNA Damage and Mutation in Population Studies

June 11-12, 2015

NIEHS Building 101, Rodbell AB
Research Triangle Park, N.C.
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Workshop on New Approaches for Detecting Environmentally-induced DNA Damage and Mutation in Population Studies

June 11-12, 2015

NIEHS Building 101, Rodbell AB
111 TW Alexander Drive, Research Triangle Park, N.C.

The purpose of this workshop is to bring together developers of tools and methods for measuring DNA repair capacity, DNA damage, and DNA mutations linked to environmental stressors with population and clinical researchers to provide guidance for new, translational directions. The panel will consider the practical issues and roadblocks to applying new approaches to studies of environmentally-related diseases and recommend solutions. The panel will also discuss strategies for increasing collaborations among basic and population-based researchers.

**Agenda**

**Thursday, June 11**

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| 8:30 a.m. | **Introduction**  
Gwen Collman, Director, Division of Extramural Research and Training, NIEHS |
| 8:40 a.m. | **Charge for the Meeting**  
Dan Shaughnessy, Exposure, Response, and Technology Branch, DERT, NIEHS |

**Session One:** New Approaches for Detecting DNA Damage  
Moderator – Guo-Min Li, University of Kentucky

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| 8:45 a.m. | **Overview: Applying New Tools for Assessing DNA Damage and Response in Human Populations**  
Leona Samson, Massachusetts Institute of Technology |
| 9:15 a.m. | **Higher Throughput Comet Assay Enables Population Studies for DNA Repair Capacity**  
Bevin Engelward, Massachusetts Institute of Technology |
| 9:30 a.m. | **Quantitative Real-time DNA Repair Analysis Tools**  
Robert Sobol, University of South Alabama |
| 9:45 a.m. | **Fluorescence-based Host Cell Reactivation Assays for Measuring DNA Repair Capacity in Human Populations**  
Zac Nagel, Massachusetts Institute of Technology |
| 10:00 a.m. | **BREAK** |
| 10:15 a.m. | **High Throughput Measurement of DSB Repair Kinetics in Healthy or Exposed Human Populations**  
David Brenner, Columbia University |
Leukocytes From Patients Undergoing Diagnostic Computed Tomography (CT) Scans Can Be Used to Validate New Technologies That Measure the DNA Damage Response

Thomas Begley, SUNY Albany

10:30 a.m.  Discussion

11:00 a.m.  Lunch – NIEHS Cafeteria

Session Two:  Novel Approaches for Mutation Detection

Moderator – Kim McAllister, Genes, Environment, and Health Branch, DERT, NIEHS

12:30 p.m.  Analysis of Somatic Mutations and Epimutations by Direct Sequencing

Jan Vijg, Albert Einstein College of Medicine

1:00 p.m.  High-fidelity Characterization of Targeted and Genome-wide Mutagenesis at Single Molecule Resolution

Jason Bielas, Fred Hutchinson Cancer Research Center

1:30 p.m.  Discussion

Session Three:  DNA Repair Capacity and Mutation Detection in Human Population Studies

Moderator – Caroline Dilworth, Population Health Branch, DERT

2:00 p.m.  DNA Damage/Repair in Human Cancer Risk

Jennifer Hu, University of Miami

2:30 p.m.  Translation Relevance of the DNA Repair Assays

Margaret Spitz, Baylor College of Medicine

2:45 p.m.  The Host Cell Reactivation DNA Repair Assay in Risk of Smoking-related Cancers

Qingyi Wei, Duke University

3:15 p.m.  BREAK

3:30 p.m.  DNA Repair, Environment, and Family-based Studies

Mary Beth Terry, Columbia University

4:00 p.m.  A Cancer Susceptibility Allele, Cell Cycle Regulation and Genomic Instability: From Epidemiology to Mouse Models to Mechanisms Of Disease

Peter Stambrook, University of Cincinnati

4:30 p.m.  Discussion of the Day’s Highlights

5:00 p.m.  Adjourn

Friday, June 12

8:30 a.m.  Closed Panel Discussion

10:00 a.m.  BREAK

10:15 a.m.  Closed Panel Discussion

Noon  Adjourn
Abstracts
Thomas Begley  
SUNY Polytechnic Institute

**Activation of Multiple Components of the DNA Damage Response by Diagnostic CT Scans Detected in Patient Samples Using an Electrochemiluminescence-based Assay Platform**

In this study we have developed DNA damage response assays on an established high throughput capable electrochemiluminescence (ECL)-based platform and benchmarked the results against traditional immunoblot and g-H2AX foci measures in cell and cancer models. In an effort to test the ECL-based system in a clinical setting, we utilized leukocyte samples from patients undergoing computed tomography (CT) scans, as they deliver ~2 to 31 millisieverts (mSv) of ionizing radiation. We show that the ECL-based platform can be used to measure the basal and damage-induced levels of Ataxia telangiectasia mutated (ATM), checkpoint kinase 2 (CHK2) and phosphorylated-ATM S1981, –CHK2 T68 and -tumor protein p53 (p53) S15 in patient matched pre- and post CT scan leukocytes. Using a blinded study design we show that the ECL-based assays can consistently (94 percent of time, 15/16 patients) identify activation of the DNA damage response by diagnostic CT scans. Ultimately the results of this pilot clinical study support the idea that the ECL-based platform is applicable for use in clinical and population cohorts that study the DNA damage response.

Jason Bielas  
Fred Hutchinson Cancer Research Center

**Targeted and Genome-wide Single Molecule DNA Damage and Mutation Detection With Massively Parallel Sequencing**

Next-generation sequencing (NGS) technologies have transformed genomic research and have the potential to revolutionize clinical medicine and the quantitation of DNA repair and mutation. However, the background error rates of sequencing instruments and limitations in targeted read coverage preclude the detection of rare DNA sequence variants by NGS. I will describe a restriction-based assay, termed Random Mutation Capture (RMC), and CypherSeq; a methodology that combines double-stranded barcoding error correction and rolling circle amplification-based target enrichment to vastly improve NGS-based rare variant detection. The CypherSeq methodology involves the ligation of sample DNA into circular vectors, which contain double-stranded barcodes for computational error correction, and adapters for library preparation and sequencing. I will review the unique advantages and disadvantages of the RMC and CypherSeq assays, both of which have the ability to detect 1 mutant base among a background of at least 109 wild type base pairs.

David Brenner  
Columbia University Medical Center

**High Throughput Measurement of DSB Repair Kinetics in Healthy or Exposed Human Populations**

Despite our rapidly increasing understanding of DNA damage repair mechanisms, we seem far from being to predict global DNA repair capacity based on the status of the many genes involved in DNA repair. An alternative, functionally-based, approach is to induce DNA damage in a tissue sample (in our case by irradiating a fingerstick of blood) and then to quantify the kinetics of DNA repair by measuring the time-dependent disappearance of DSB repair foci (in our case g-H2AX). We have developed a high-throughput fully-automated system to do this, based on our RABiT (Rapid Automated Biodosimetry Tool) robot-based technology, which thus provides a practical, rapid, and inexpensive tool for assessing DNA repair capacity on an individual-by-individual basis.
Bevin Engelward  
Massachusetts Institute of Technology  

*Higher Throughput Comet Assay Enables Population Studies for DNA Repair Capacity*

The Engelward laboratory is focused on DNA damage and repair and the role that environment plays in modulating genomic instability. Recently, the Engelward laboratory collaborated with S. Bhatia to develop the “CometChip,” a high throughput version of the traditional comet assay which measures DNA damage (damage detection is based on the principle that damaged DNA migrates more readily than undamaged DNA when electrophoresed). The CometChip affords more than two orders of magnitude increase in throughput as well as significantly higher sensitivity. Using the CometChip, it is now possible to assess multiple samples for multiple time points, experiments that were virtually impossible using the traditional assay. The CometChip has been shown to be effective for detecting variations in multiple DNA repair pathways (nucleotide excision repair, base excision repair, non-homologous end-joining, and mismatch repair). Additionally, the CometChip has been used as a tool to measure repair kinetics for two dozen lymphoblastoid cells from ethnically diverse people. Given its throughput, versatility and sensitivity, the CometChip opens doors to exciting new population studies.

Jennifer Hu  
University of Miami School of Medicine  

*DNA Damage/Repair in Cancer Etiology and Precision Medicine*

The long-term goal of our research is to improve radiotherapy-related quality of life, clinical outcomes, and overcome breast cancer disparities. The presentation will focus on DNA damage/repair in cancer etiology and precision medicine. The objective is to advance our scientific knowledge in the accurate assessment of prognosis and response to therapy in cancer patients, which will pave the ways for precision intervention/therapies, and ultimately improve quality of life and clinical outcomes in cancer survivors.

Zachary Nagel  
Massachusetts Institute of Technology  

*Fluorescence-based Host Cell Reactivation Assays for Measuring DNA Repair Capacity in Human Populations*

We have developed cell-based assays for simultaneously measuring DNA repair capacity in multiple pathways. In addition to canonical host cell reactivation assays, wherein reporter protein expression depends upon repair of transcription blocking lesions, we have developed new assays that report on transcriptional mutagenesis induced by DNA lesions, thus extending the scope of host cell reactivation assays to include lesions that are bypassed by RNA polymerase in cells. We have applied multiplexed host cell reactivation assays to a panel of lymphoblastoid cell lines, and we have shown that DNA repair capacity in multiple pathways predicts the sensitivity of cells to killing with DNA damaging agents. These functional assays hold promise for measuring DNA repair capacity in large populations with the goal of personalized disease prevention for individuals with aberrant DNA repair capacity in normal tissues, and personalized cancer therapy based on DNA repair capacity in cancer cells.

Robert Sobol  
University of South Alabama Mitchell Cancer Institute  

*Quantitative Real-time DNA Repair Analysis Tools*

Essential to the development of specific DNA repair inhibitors is the availability of robust, highly sensitive assays to measure DNA repair capacity. This presentation will detail our current and ongoing efforts to optimize our DNA Repair Molecular Beacons. These quantitative assays are amenable to multiplexing and provide a rapid, high-throughput method for the discovery and validation of DNA repair inhibitors and will be a valuable platform for functional DNA Repair measurements and biomarker analysis of cell/tumor lysates or tissue aspirates.
Margaret Spitz  
Baylor College of Medicine  

_Translation Relevance of the DNA Repair Assay_

DNA repair capacity is a two-edged sword. Suboptimal repair is associated with increased cancer risk; but may also be predictive of better response to certain chemotherapies. Platinum chemotherapeutic agents are used to treat a variety of cancers; however their efficacy is limited by the development of resistance. NER pathway is a key pathway that removes bulky DNA adducts induced by platinum and other DNA damaging chemotherapeutic agents. For example, ERCC1 mRNA levels in tumor samples from patients with ovarian, colorectal and non–small cell lung cancer are inversely correlated with response to platinum therapy. Likewise efficient DNA repair capacity as measured by the host cell reactivation assay is associated with poorer survival outcome. These and other examples may provide insight into the molecular mechanisms of response and resistance to chemotherapy and contribute to advancing the concept of precision medicine.

Peter Stambrook  
University of Cincinnati  

_A Cancer Susceptibility Allele, Cell Cycle Regulation and Genomic Instability: From Epidemiology to Mouse Models to Mechanisms of Disease_

The checkpoint kinase CHEK2 (Chk2 in mouse) is an active participant in regulating cell cycle progression after damage and plays a role in repair of double strand DNA breaks. Following DNA damage caused by ionizing radiation, CHEK2 is phosphorylated and activated by ATM, and in turn phosphorylates the bifunctional phosphatase CDC25A, priming the latter for proteasome-mediated degradation which contributes to a G1/S arrest. In addition, CHEK2 phosphorylates BRCA2 on its carboxy end, an event that is important for the release of Rad 51 that is bound to BRCA2 and for recruitment of Rad 51 to sites of DNA damage. Not surprisingly, some CHEK2 variants increase the risk of certain cancer types, including breast cancer. A large number of CHEK2 mutations and variants have been described, including transitions, transversions, and mutations that cause protein truncation. The CHEK2*1100delC variant has a single nucleotide deletion at position 1100 which forms a stop codon and results in the loss of most of the kinase domain. The frequency with which this variant is found appears to vary according to ethnic group and locale. Epidemiologic studies have shown that women who harbor this variant have an elevated risk of breast cancer. To better understand the biology of CHEK2 and the CHEK2*1100delC variant, we generated a knockin mouse in which the cytosine at position 1100 was deleted to produce a genetically modified mouse that mimics the human CHEK2*1100delC condition. The Chk2*1110delC homozygous mouse spontaneously developed tumors, but not until after about one year, but only female mice were affected. Male mice did not develop tumors above the background level displayed by wildtype animals. When challenged with DMBA or when bred into a background in which the RON receptor was over expressed, the rate of tumor formation was accelerated, indicating that genetic modifiers and environmental exposure can enhance the tumorigenic phenotype of the CHEK2*1100delC cancer susceptibility allele.
Mary Beth Terry  
Columbia University Mailman School of Public Health  
**DNA Repair, Environment, and Family-based Studies**

Many causal genes for cancer have been found from family-based studies while many established environmental risk factors for cancer have been discovered through studies of unrelated individuals. Epidemiologic evidence suggests that some environmental factors modify breast cancer risk for women with a family history. Most epidemiology studies, however, record only first-degree family history as a binary factor, which does not capture the potential importance of disease in second-degree and more distant relatives, and rarely take into account the importance of age at diagnosis of affected relatives. One approach to studying gene-environment interactions is to consider family-based studies that span the continuum of absolute risk. In this talk, we discuss findings from our family-based studies and implications of using family-based designs to specifically understand the role of DNA repair phenotype in breast cancer risk. We also present data on environmental modifiers of BRCA1 and BRCA2 mutations. We end by discussing the promise of using selected DNA repair phenotype assays for risk assessment in high-risk women.

Jan Vijg  
Albert Einstein College of Medicine  
**Analysis of Somatic Mutations and Epimutations by Direct Sequencing**

Genomes are inherently unstable due to the evolutionary need for genetic variants as substrates for natural selection. Genome diversity is driven by errors made in processing DNA damage during replication or repair. This can result in a variety of DNA sequence and epigenetic changes, including base pair substitutions, genome structural variations and alterations in DNA methylation or histone modification. In contrast to DNA damage itself, such changes in the DNA information content are irreversible. While rapid advances in genome sequencing has now made it fairly easy to identify DNA mutations and epimutations between individuals or in clonal lineages, such as tumors, the load of somatic mutations and epimutations in aging tissues has remained virtually inaccessible due to their extremely low abundance. Collectively, however, accumulating mutations and epimutations could underlie late-life tissue dysfunction and age-related diseases, including non-neoplastic disease. We developed various assays to quantitatively analyze aging cells and tissues for low-frequency (epi)mutagenic events based on next-generation sequencing. Using these assays we are currently beginning to elucidate the landscape of mutations and epimutations in different tissues and organisms during aging.

Qingy Wei  
Duke University  
**The Host Cell Reactivation DNA Repair Assay in Risk of Smoking-related Cancers**

DNA repair is a complicated biological process, consisting of several distinct pathways, that plays a fundamental role in the maintenance of genomic integrity. The very important field of DNA repair and cancer risk has developed rapidly in the past decades. During this time period, we conducted the studies of DNA repair capacity (DRC) phenotypic markers for nucleotide excision repair (NER), as measured by the benzo(a)pyrene diol epoxide (BPDE)/ultraviolet (UV)-induced mutagen sensitivity (chromatid break) assay, BPDE-induced adduct assay, and host cell reactivation (HCR)-DRC assay. We performed these assays with peripheral blood lymphocytes in a series of molecular epidemiological studies of lung cancer and head and neck cancer, in addition to our early skin cancer studies. Results of our studies suggest that individuals with reduced DRC have an elevated cancer risk.
Biographies
Thomas Begley
SUNY Polytechnic Institute

Thomas Begley is an associate professor of nanobiosciences at the Colleges of Nanoscale Science and Engineering at the SUNY Polytechnic Institute. Begley holds a doctorate from the University at Albany – SUNY and did fellowships in cancer biology and biological engineering at Harvard and MIT. Begley's scientific work has been focused on cellular responses to DNA damage and their control of DNA repair pathways. He has developed systems biology and computational approaches to study transcriptional and translational responses to DNA damage. His lab has developed animal models to study the role of translational regulation of damage response proteins in disease prevention. In addition, his lab has developed technology solutions to study the DNA damage response in clinical samples. These projects have identified novel regulators of stress response systems and new technologies for use in population studies, and they have potential applications in cancer diagnostics and therapeutics.

Jason Bielas
Fred Hutchinson Cancer Research Center

Jason Bielas is an associate member in the Translational Research Program at Fred Hutchinson Cancer Research Center (FHCRC) and holds an affiliate associate professorship in Department of Pathology at the University of Washington. Bielas has had a long-standing interest and commitment to discerning the relationship between mutagenesis, aging, and cancer. Bielas earned his doctorate with distinction and the Governor General of Canada's Gold Medal in 2004 from the Department of Biology at York University in Toronto. Together with doctoral thesis advisor, John Heddle, Ph.D., he developed novel methods to measure DNA repair and mutation to delineate the relationship between proliferation and mutagenesis. Following his doctoral work, Jason pursued postdoctoral training in the laboratory of Lawrence Loeb. Here, at the University of Washington, Bielas' primary research focused on the role of a mutator phenotype in carcinogenesis, where he continued to develop novel methods to monitor mutagenesis, including the Random Mutation Capture (RMC) assay, which demonstrates that tumors exhibit point mutation instability (PIN), and that mitochondrial point mutations do not limit natural lifespan. During his tenure as graduate student and postdoctoral fellow, Bielas received a number of awards, including a graduate scholarship from the Natural Sciences and Engineering Research Council of Canada (NSERC), an Ontario Graduate Scholarship in Science and Technology, the RH Haynes Scholarship for Academic Excellence, and postdoctoral fellowships from NSERC, the Canadian Institutes of Health Research, and the Terry Fox Foundation. Since opening his laboratory at the FHCRC, Jason has received a New Scholar Award from the Ellison Medical Foundation, a New Investigator Award from the Department of Defense, and an Outstanding New Environmental Scientist (ONES) (RO1) Award from the National Institute of Environmental Health Sciences.

David Brenner
Columbia University Medical Center

David Brenner is the director of the Columbia University Center for Radiological Research in New York, which was founded in 1915 by Gioacchino Failla, a graduate student of Marie Curie. Brenner divides his research time between the effects of high doses of ionizing radiation (relating to radiation therapy) and the effects of low doses of radiation (relating to radiological, environmental, and occupational exposures). At low doses, he studies approaches and uncertainties associated with quantitative radiation risk assessment. At high doses, his proposal to use small numbers of large radiotherapy doses to treat prostate cancer is increasingly being used in the clinic. In addition, he is principal investigator of the Center for High-throughput Minimally-invasive Radiation Biodosimetry.

Brenner has published more than 300 peer-reviewed papers. In addition, he is the author of two books on radiation for the lay person: "Making the Radiation Therapy Decision" and "Radon, Risk, and Remedy." He is a recent recipient of the Failla Gold Medal, the annual award given by the Radiation Research Society for contributions to radiation research, as well as the Weldon Memorial Prize for development of mathematical or statistical methods as applied to problems in biology. He currently serves on the National Academies Nuclear and Radiation Studies Board.
Bevin Engelward  
Massachusetts Institute of Technology

Bevin Engelward is a professor of biological engineering at MIT. Engelward’s research career started at a Yale laboratory. Her laboratory was the first to create a mouse model in which rare homologous recombination-driven sequence changes can be detected by a fluorescent signal. Her laboratory, in collaboration with S. Bhatia, has also developed the “CometChip” technology, which enables high throughput studies of DNA damage and repair in human cells. Trevigen Inc. is developing the CometChip as a commercial product that will soon be available. Engelward is currently the president-elect for the Environmental Mutagenesis and Genomics Society, and she is deputy director of the MIT Center for Environmental Health Sciences.

Jennifer Hu  
University of Miami School of Medicine

Jennifer Hu serves as a professor of public health sciences, biochemistry and molecular biology, and human genetics and genomics at the University of Miami Miller School of Medicine. The research highlights from Hu’s laboratory and collaborative effort that has significant impact on the cancer research field include: (1) deficient DNA repair and elevated DNA damage in human breast and prostate cancer risk; (2) racial/ethnic specific polygenic models of DNA repair in human cancer risk and somatic mutations; (3) functional implication of DNA repair genotypes in human cancer risk and targeted therapies; (4) gene-diet interactions in human colon and breast cancer risk; and (5) genome-wide association studies of novel breast cancer and ER-negative breast cancer susceptibility loci in women of African ancestry. Her current research program mainly focuses on breast cancer disparities related to etiology, treatment responses, and clinical outcomes. Her long-term research goals are to improve quality of life and clinical outcomes, and ultimately overcome breast cancer disparities. She will apply newly developed genotyping/phenotyping assays for DNA damage/repair as well as other “omic” technologies to evaluate treatment-induced adverse reactions and recurrence in a large tri-racial/ethnic breast cancer population. Investigating this new paradigm will develop powerful tools in identifying high-risk populations and targets for precision interventions and therapies. The outcomes will pave the ways for precision intervention/therapies, and ultimately improve quality of life and clinical outcomes in cancer survivors, particularly in underserved minorities with more aggressive disease and worse clinical outcomes.

Zachary Nagel  
Massachusetts Institute of Technology

Zachary Nagel received a doctorate in chemistry from the University of California, Berkeley, where he studied the role of protein motion and hydrogen quantum tunneling in extremophilic enzymes in the laboratory of professor Judith Klinman. Nagel’s postdoctoral research has focused on the development of high throughput DNA repair assays in professor Leona Samson’s laboratory at MIT in the Department of Biological Engineering. This work lead to quantitative, multiplexed, cell-based assays for DNA repair capacity in multiple pathways. As an independent researcher, Nagel plans to combine biochemical and biophysical tools with the newly developed DNA repair assays to understand mechanisms of chemoresistance in cancer, and to develop personalized cancer prevention and treatment strategies.
**Leona Samson**  
Massachusetts Institute of Technology

Leona Samson is currently an American Cancer Society professor and the Uncas and Helen Whitaker professor in the Department of Biological Engineering and the Department of Biology at MIT. She earned her bachelor’s degree in biochemistry from the University of Aberdeen in Scotland, and her doctorate in molecular biology from the Imperial Cancer Research Fund and University College, London University in England (with John Cairns). She received postdoctoral training at UCSF (with James Cleaver), and UC Berkeley (with Stuart Linn). Following 18 years on the faculty of the Harvard School of Public Health, she joined MIT in 2001, where she directed the Center for Environmental Health Sciences until 2012. Samson’s research has focused on how cells, tissues, and animals respond to environmental toxicants using a diverse set of approaches including, x-ray crystallography, biochemistry, molecular biology, systems biology, microbial genetics, somatic cell genetics, mouse genetics using knockout and transgenic technology, gene therapy, genomics, and human population-based studies.

**Robert Sobol**  
University of South Alabama Mitchell Cancer Institute

Robert Sobol is a professor in the departments of oncologic sciences and pharmacology at the University of South Alabama (USA) and is the chief of the Molecular and Metabolic Oncology Program at the USA/Mitchel Cancer Institute (MCI). In addition, Sobol is the director of the Gene Expression, Engineering, and Discovery lab, a core facility for the development of lentiviral vectors for gene expression (cDNA, shRNA), gene editing (CRISPR), and gene discovery; and director of the MCI Technology Development Facility. Research in the Sobol lab focuses on the mechanism of base excision repair, PARP, and NAD+ metabolism in human cells and the convergent role of these enzymes and pathways in response to chemotherapy. A major goal in the lab is to use biochemical, genetic, and imaging modalities to study the protein complexes of the base excision repair pathway that respond to DNA damage induced by chemotherapy and how this pathway affects the regulation of cellular metabolism via ADP-ribosylation signaling and alterations in NAD+ metabolism. Major techniques used in the Sobol lab involve the analysis of cellular response to stress, with an emphasis on DNA repair, cell death, and the DNA damage response, the manipulation of cells in culture using lentivirus for cDNA expression, RNA interference (shRNA) or gene Knock-out and Knock-in (CRISPR), and the development of stable, isogenic cell lines. Further, the lab focuses on the development of technologies to evaluate DNA repair, DNA damage, and cell death in human cells, stem cells, and diseased and healthy human tissue.

**Margaret Spitz**  
Baylor College of Medicine

Margaret Spitz is a professor at the Dan L. Duncan Cancer Center at Baylor College of Medicine, where she provides strategic direction for its population sciences program. Prior to her appointment at Baylor, she had a 27-year history on faculty at MD Anderson Cancer Center in Houston, Texas, serving as founding chair of the Department of Epidemiology. Spitz earned her medical degree from the University of Witwatersrand Medical School in Johannesburg, South Africa, and her Master of Public Health from The University of Texas School of Public Health. Spitz has a long standing interest in genetic susceptibility to lung cancer. She has developed a lung cancer risk prediction model, has participated in lung cancer GWAS, and is a founding member of the International Lung Cancer Consortium. She has outlined an integrative approach to extend the boundaries of molecular cancer epidemiology by integrating modern and rapidly evolving “omics” technologies into state-of-the-art molecular epidemiology in order to comprehensively explore the mechanistic underpinnings of epidemiologic observations into cancer risk and outcome. Spitz has been a recipient of numerous honors, most recently the Association of American Cancer Institutes’ Distinguished Scientist Award. She has served as co-chair of the National Cancer Institute’s Lung Cancer Progress Review Group and was a member of its Board of Scientific Advisors. She also participates in the external scientific advisory committees of several major cancer centers.
Peter Stambrook
University of Cincinnati

Peter Stambrook is the former Francis Brunning professor and chair of the Department of Cell and Cancer Biology at the University of Cincinnati College of Medicine. He is currently distinguished research professor in the Department of Molecular Genetics. Stambrook’s long term interests have focused around mutagenesis, DNA replication, DNA repair, and preservation of genomic stability in somatic cells in vivo and in embryonic stem (ES) cells. In this context, he has directed an NIEHS training grant entitled, “Environmental Carcinogenesis and Mutagenesis” for more than 26 years and has held grants from NIGMS, NINDS, NCI, and NIEHS. He also served as the director of the University of Cincinnati component of the NIEHS Comparative Mouse Genomics Centers Consortium (CMGCC) and as the chair of its steering committee. Among his honors, Stambrook includes a Senior Fogarty Fellowship from the NIH, election as a fellow of the American Association for the Advancement of Science (AAAS), election as president of the Environmental Mutagen Society (now the Environmental Mutagenesis and Genomics Society) and that society’s award for research. He was recently elected as president-elect of the Society for Experimental Biology and Medicine (SEBM) and is the recipient of the SEBM Distinguished Scientist Award.

Stambrook has served as the chair of the Scientific Review Panel for the Israel Cancer Research Fund and is the chair of its International Scientific Council. He is an associate editor of Experimental Biology and Medicine and recently stepped down as editor-in-chief of Mutation Research: Fundamental and Molecular Mechanisms. Among his more memorable service experiences are his service as a member of the Alexander Hollaender program which provides educational workshops and lectures in scientifically underdeveloped countries and which brought him to lands as diverse as Colombia and Kazakhstan.

Mary Beth Terry
Columbia University Mailman School of Public Health

Mary Beth Terry, Ph.D., focuses her research on breast cancer and in the molecular epidemiology and lifecourse methods of the disease, in particular. She is a cancer epidemiologist with over 15 years of leading studies of breast cancer etiology specifically focused on the role of genetics, epigenetics, and other biomarkers play in modifying the effects of environmental exposures. Terry currently leads four NIH grants through the National Cancer Institute and the National Institute for Environmental Health Sciences that focus on following cancer risk within family-based cohorts. She is also funded through the Breast Cancer Research Foundation. Terry has authored or co-authored over 200 scientific publications. Her more recent work studying biomarkers, which can be modified throughout life, supports that selected markers of DNA methylation and other biomarkers are associated with breast cancer risk even within high risk families. Understanding whether biomarkers can help explain risk in higher risk women is important as only a minority of women with a family history of cancer carry the BRCA1 or BRCA2 mutation. Her work also focuses on measuring risk factors for mammographic density, a strong intermediate marker of breast cancer. In addition to her doctorate in epidemiology, Terry has a master’s degree in economics and previously worked as an econometrician and program evaluator for a number of government-sponsored programs. Terry teaches introductory and advanced epidemiologic methods at the Mailman School of Public Health.
Jan Vijg
Albert Einstein College of Medicine

Jan Vijg is professor and chairman of the Department of Genetics at the Albert Einstein College of Medicine in New York. The Vijg lab's main research interest is to understand the role of DNA mutations and epimutations in human aging and disease. In the past the Vijg group developed transgenic mouse models for studying mutagenesis in vivo (MutaMouse; 1989) and used these models extensively for testing the impact of somatic mutations on aging. The lab is currently developing novel, genome-wide approaches to directly measure various types of genome instability in primary cells and tissues. The methods that are being explored include single-cell, whole genome sequencing to study somatic mutations and epimutations in relation to changes in the transcriptome, as well as new computational procedures to characterize genome structural variation in relation to changes in gene regulatory networks.

Qingy Wei
Duke University

Qingyi Wei is professor of medicine at Duke Cancer Institute, Duke University Medical Center. The Wei lab's core goal is to identify biomarkers for genetic susceptibility to cancer. Wei's scientific work has been focused on developing genotyping and phenotyping of genes involved in DNA repair to accomplish that goal. By using peripheral blood samples in molecular epidemiology studies, Wei's lab perform cell-culture assays to quantitatively measure DNA repair capacity for nucleotide excision repair phenotype and gene expression at levels of mRNA and repair proteins as well as identifying genetic variants that have an effect of the measured phenotypes. With specific interest in environmentally induced cancers, Wei's studies focus on sunlight-induced skin cancers and tobacco-induced lung cancer and head and neck cancer. In his approach of molecular epidemiology studies, he performs multivariate statistical modeling for cancer risk associated with these biomarkers as well as assesses the role played by gene-environment interactions. The ultimate goal of his research is to identify subpopulation at cancer risk for earlier detection and prevention of cancer.
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Suggested Reading


• Mutamba, JT, Svilar, D, Prasongtanakij, S, Wang, XH, Lin, YC, Dedon, PC, Sobol, RW, Engelward, BP. “XRCC1 and Base Excision Repair Balance in Response to Nitric Oxide” (2011) DNA Repair, 10: 1282-1293; PMID: 22041025; PMCID: PMC3593656.


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