Division of Intramural Research

NAEHS Council Update

February 2013

DIR RECRUITMENTS

Director, Clinical Research Program

The NIEHS is searching for a senior investigator to direct its Clinical Research Program. The Director, Clinical Research Program, is responsible for the development, administration, coordination and oversight of investigator-initiated clinical research; provides general advice to the Director and Scientific Director, NIEHS, on matters relating to human and clinical studies; supervises the Office of Research Compliance; and develops policies and programs for the execution of clinical research at NIEHS. The Clinical Director is responsible for creating and maintaining a research environment in which clinical findings influence the direction of laboratory studies and laboratory findings are applied back to the clinical and clinical research communities. The incumbent will facilitate intramural clinical research by identifying opportunities for translating basic science into clinical studies. The Clinical Director will ensure that Institute research reflects the highest standards of scientific excellence and ethical conduct for the protection of human subjects. The incumbent will review matters pertaining to the provision of patient care in research protocols and oversee research allocation, scientific review, and recruitment of staff. The Clinical Director will provide advice and training on the conduct of clinical studies, facilitate clinical research collaborations between intramural and extramural investigators, and develop long-range clinical research goals and objectives relevant to the mission of NIEHS. It is expected that the successful candidate will oversee a personal clinical research program that will involve some combination of outpatient oriented studies within the Clinical Research Unit, epidemiological studies, basic laboratory studies, or inpatient studies at the Clinical Research Center in Bethesda. Emphasis will be placed upon investigators with a primary research interest in clinical research; however, the selected candidate may have a modest independent basic laboratory research program, particularly if the basic research intersects with the candidate's clinical studies. Dr. Carter Van Waes, Clinical Director, National Institute on Deafness and Other Communication Disorders, is chair of the search committee.

NEW HIRES AND CHANGES IN DIR LEADERSHIP

Comparative Medicine Branch
Dr. Kathy Laber will be joining NIEHS as Chief of the Comparative Medicine Branch, Attending Veterinarian, and Animal Program Director. Currently, Dr. Laber is a Professor in the Department of Comparative Medicine at the Medical University of South Carolina, and Director of the Animal Resource Program for the Ralph H. Johnson Medical Center. Dr. Laber received her D.V.M. in 1984 from Michigan State University and completed her residency in Laboratory Animal Medicine at Bowman Gray School of Medicine. She also completed a Masters in Molecular and Cellular Pathobiology from Wake Forest University in 1988. Dr. Laber has been active in many national and international organizations within her field. She is the immediate Past-President of the American Association of Laboratory Animal Science Association (AALAS), an educational organization that serves a membership of 13,000 professionals dedicated to supporting quality animal research. Dr. Laber served as President of the Association for the Assessment and Accreditation of Laboratory Animal Care International (AAALAC). In her 16 years with AAALAC she conducted more than 170 site visits in the U.S. and abroad. She has also served on the American College of Laboratory Animal Medicine and the Association of Veterans Affairs Veterinary Medical Officers. She will begin work in June 2013.

Laboratory of Structural Biology
Upon the request of Dr. Thomas Kunkel to relinquish his role as Chief, Laboratory of Structural Biology (LSB), effective September 30, 2012, Dr. Traci Hall agreed to assume the role of Acting Chief, LSB, beginning October 1, 2012. Dr. Hall is leader of the Macromolecular Structure Group, which studies the molecular basis of specificity in RNA regulatory pathways and how such specificity can modulate coordinated responses to environmental stressors. She was appointed in 1998 as the first tenure-track investigator of LSB and achieved tenure in 2004. She has served on the NIEHS Assembly of Scientists (AoS) Council and was the President of AoS in 2010. She was also a member of the Scientific Director's Advisory Committee from 2009-2011 and played a key role on the DIR Retreat/Strategic Implementation Plan subcommittee of the DIR Council.

Clinical Research Unit
Dr. Shepherd Schurman has been hired as a Staff Clinician at the NIEHS Clinical Research Unit (CRU). Dr. Schurman comes to NIEHS from the National Institute on Aging (NIA). At NIA Dr. Schurman worked with the Baltimore Longitudinal Study of Aging where he started working with DNA repair and polymorphisms associated with age-related diseases. Prior to joining NIA Dr. Schurman was a research fellow at National Human Genome Research Institute studying gene therapy and immune deficiency disorders. In addition to his role as a staff clinician in the CRU, he will head of the Environmental Polymorphisms Registry (EPR).

Office of Clinical Research
Dr. Stavros Garantziotis has agreed to serve as Acting Clinical Director. Dr. Garantziotis is medical director of the NIEHS Clinical Research Unit and is the leader of the Matrix Biology Group in the Laboratory of Respiratory Biology. The Matrix Biology Group studies cell-matrix interactions in the pulmonary response to environmental or alloimmune lung injury. Dr.

Garantziotis joined NIEHS in August 2007. Prior to joining NIEHS he was Clinical Instructor in the Division of Pulmonary, Allergy and Critical Care Medicine at Duke University.

DIR RESEARCH UPDATE

Bioinformatics in Environmental Health Science Research

Leping Li, Ph.D.

Biostatistics Branch, DIR, NIEHS

Bioinformatics is an integral part of environmental health science research. My main research focus is the development and application of computational/statistical methods for identifying functional elements in DNA sequences. I will give an example of how a computational analysis facilitates new discovery and hypothesis generation.

We are also developing methods and tools for the analysis of next-generation sequencing (NGS) data. DIR and DNTP scientists are generating increasingly large amounts NGS data in their efforts to understand fundamental biological processes and to elucidate how biological systems (e.g., cells or tissues) respond to environmental toxicants. One area of great interest to us is the development of statistical/ computational methods that detect differential changes not only in gene expression but also in splicing patterns from mRNA-seq data. Tools for detecting differential splicing could have a major impact in toxicogenomics, as examples exist where changes or imbalances in isoforms have been implicated in tumor development.

NIEHS SCIENCE DAY

The Tenth Annual NIEHS Science Day was held on November 1-2, 2012, at the Rall Building on the NIEHS Campus to celebrate the achievements of NIEHS scientists. The event was open to the public and more than 250 attendees from universities and research institutions in the Triangle Area attended. NIEHS Science Day consisted of a mini-symposium on Stem Cells in Environmental Health Science in which presentations were given by scientists in DIR, DNTP and DERT, a presentation by a former NIEHS trainee, 12 oral presentations given by fellows, students, and technicians, 101 poster presentations and an Awards Ceremony. Judging for the awards was done by Extramural Scientists from universities and research organizations in the Triangle Area, Intramural Scientists and the NIEHS Trainees Assembly.

Mentor of the Year: E. Mitchell Eddy, Ph.D., Laboratory of Reproductive and Developmental Toxicology

Fellow of the Year: Bonnie R. Joubert, Ph.D., Epidemiology Branch

Best Poster Presentation:

1. Margret A. Adgent, Ph.D., Epidemiology Branch, "Cytological assessment of urethral and vaginal epithelium in 1 and 12-week old infants: evidence for postnatal estrogen withdrawal using swab and urine cell collection methods."
2. Kymberly M. Gowdy, Ph.D., Laboratory of Respiratory Biology, "A major lipid raft protein flotillin 2 regulates T cell function and allergic asthma."
3. Seddon Y. Thomas, Ph.D., Laboratory of Respiratory Biology. "A strategy for fate mapping of IL-17-producing cells in vivo."

Best Oral Presentation: George J. Fromm Jr., Ph.D., Laboratory of Molecular Carcinogenesis, "NELF mediated pausing of RNA polymerase II fine-tunes Mapk/ERK signaling and controls stem cell pluripotency."

DIR PAPERS OF THE YEAR FOR 2012

Panigrahy D, Edin ML, Lee CR, Huang S, Bielenberg DR, Butterfield CE, Barnés CM, Mammoto A, Mammoto T, Luria A, Benny O, Chaponis DM, Dudley AC, Greene ER, Vergilio JA, Pietramaggiori G, Scherer-Pietramaggiori SS, Short SM, Seth M, Lih FB, Tomer KB, Yang J, Schwendener RA, Hammock BD, Falck JR, Manthati VL, Ingber DE, Kaipainen A, D'Amore PA, Kieran MW, Zeldin DC. Epoxyeicosanoids stimulate multiorgan metastasis and tumor dormancy escape in mice. *J. Clin. Invest*., 122: 178-191, 2012.

Epoxyeicosatrienoic acids (EETs) are small molecules produced by cytochrome P450 epoxygenases. They are lipid mediators that act as autocrine or paracrine factors to regulate inflammation and vascular tone. As a result, drugs that raise EET levels are in clinical trials for the treatment of hypertension and many other diseases. However, despite their pleiotropic effects on cells, little is known about the role of these epoxyeicosanoids in cancer. Here, using genetic and pharmacological manipulation of endogenous EET levels, we demonstrate that EETs are critical for primary tumor growth and metastasis in a variety of mouse models of cancer. Remarkably, we found that EETs stimulated extensive multiorgan metastasis and escape from tumor dormancy in several tumor models. This systemic metastasis was not caused by excessive primary tumor growth but depended on endothelium-derived EETs at the site of metastasis. Administration of synthetic EETs recapitulated these results, while EET antagonists suppressed tumor growth and metastasis, demonstrating in vivo that pharmacological modulation of EETs can affect cancer growth. Furthermore, inhibitors of soluble epoxide hydrolase (sEH), the enzyme that metabolizes EETs, elevated endogenous EET levels and promoted primary tumor growth and metastasis. Thus, our data indicate a central role for EETs in tumorigenesis, offering a mechanistic link between lipid signaling and cancer and emphasizing the critical importance of considering possible effects of EET-modulating drugs on cancer.

Miao YL, Stein P, Jefferson WN, Padilla-Banks E, Williams CJ. Calcium influx-mediated signaling is required for complete mouse egg activation. *Proc. Natl. Acad. Sci. USA*., 109: 4169-4174, 2012.

Mammalian fertilization is accompanied by oscillations in egg cytoplasmic calcium (Ca^{2+}) concentrations that are critical for completion of egg activation. These oscillations are initiated by Ca^{2+} release from inositol 1,4,5-trisphosphate (IP_3)-sensitive intracellular stores. We tested the hypothesis that Ca^{2+} influx across the plasma membrane was a requisite component of egg activation signaling, and not simply a Ca^{2+} source for store repletion. Using intracytoplasmic sperm injection (ICSI) and standard in vitro fertilization (IVF), we found that Ca^{2+} influx was not required to initiate resumption of meiosis II. However, even if multiple oscillations in intracellular Ca^{2+} occurred, in the absence of Ca^{2+} influx, the fertilized eggs failed to emit the second polar body, resulting in formation of three pronuclei. Additional experiments using the Ca^{2+} chelator, BAPTA/AM, demonstrated that Ca^{2+} influx is sufficient to support polar body emission and pronucleus formation after only a single sperm-induced Ca^{2+} transient, whereas BAPTA/AM-treated ICSI or fertilized eggs cultured in Ca^{2+}-free medium remained arrested in metaphase II. Inhibition of store-operated Ca^{2+} entry had no effect on ICSI-induced egg activation, so Ca^{2+} influx through alternative

channels must participate in egg activation signaling. Ca^{2+} influx appears to be upstream of CaMKIIγ activity because eggs can be parthenogenetically activated with a constitutively active form of CaMKIIγ in the absence of extracellular Ca^{2+}. These results suggest that Ca^{2+} influx at fertilization not only maintains Ca^{2+} oscillations by replenishing Ca^{2+} stores, but also activates critical signaling pathways upstream of CaMKIIγ that are required for second polar body emission.

Gilchrist DA, Fromm G, dos Santos G, Pham LN, McDaniel IE, Burkholder A, Fargo DC, Adelman K. Regulating the regulators: the pervasive effects of Pol II pausing on stimulus-responsive gene networks. *Genes Dev*., 26: 933-944, 2012.

The expression of many metazoan genes is regulated through controlled release of RNA polymerase II (Pol II) that has paused during early transcription elongation. Pausing is highly enriched at genes in stimulus-responsive pathways, where it has been proposed to poise downstream targets for rapid gene activation. However, whether this represents the major function of pausing in these pathways remains to be determined. To address this question, we analyzed pausing within several stimulus-responsive networks in Drosophila and discovered that paused Pol II is much more prevalent at genes encoding components and regulators of signal transduction cascades than at inducible downstream targets. Within immune-responsive pathways, we found that pausing maintains basal expression of critical network hubs, including the key NF-κB transcription factor that triggers gene activation. Accordingly, loss of pausing through knockdown of the pause-inducing factor NELF leads to broadly attenuated immune gene activation. Investigation of murine embryonic stem cells revealed that pausing is similarly widespread at genes encoding signaling components that regulate self-renewal, particularly within the MAPK/ERK pathway. We conclude that the role of pausing goes well beyond poising-inducible genes for activation and propose that the primary function of paused Pol II is to establish basal activity of signal-responsive networks.

Roberts SA, Sterling J, Thompson C, Harris S, Mav D, Shah R, Klimczak LJ, Kryukov GV, Malc E, Mieczkowski PA, Resnick MA, Gordenin DA. Clustered mutations in yeast and in human cancers can arise from damaged long single-strand DNA regions. *Mol. Cell*, 46: 424-435, 2012.

Mutations are typically perceived as random, independent events. We describe here nonrandom clustered mutations in yeast and in human cancers. Genome sequencing of yeast grown under chronic alkylation damage identified mutation clusters that extend up to 200 kb. A predominance of "strand-coordinated" changes of either cytosines or guanines in the same strand, mutation patterns, and genetic controls indicated that simultaneous mutations were generated by base alkylation in abnormally long single-strand DNA (ssDNA) formed at double-strand breaks (DSBs) and replication forks. Significantly, we found mutation clusters with analogous features in sequenced human cancers. Strand-coordinated clusters of mutated cytosines or guanines often resided near chromosome rearrangement breakpoints and were highly enriched with a motif targeted by APOBEC family cytosine-deaminases, which strongly prefer ssDNA. These data indicate that hypermutation via multiple simultaneous changes in randomly formed ssDNA is a general phenomenon that may be an important mechanism producing rapid genetic variation.

Fei C, Deroo LA, Sandler DP, Weinberg CR. Fertility drugs and young-onset breast cancer: results from the Two Sister Study. *J. Natl. Cancer Inst*., 104: 1021-1027, 2012.

BACKGROUND: Fertility drugs stimulate hyperovulation, which may have implications for breast cancer. We examined the association between use of fertility drugs (clomiphene citrate [CC] and follicle-stimulating hormone [FSH]) and subsequent risk of young-onset (<50 years at diagnosis) breast cancer.
METHODS: We conducted the Two Sister Study, a sister-matched case-control study, by enrolling 1422 women between September 2008 and December 2010, who were younger than age 50 years at diagnosis with breast cancer and were enrolled within 4 years of diagnosis, and 1669 breast cancer-free control sisters from the Sister Study. Participants reported their use of fertility drugs (CC and FSH) and ever-users reported whether a pregnancy had resulted that lasted 10 or more (10+) weeks. Conditional logistic regression was used to estimate confounder-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for fertility drug use with or without conception of a 10+ week pregnancy.
RESULTS: A total of 288 participants reported having used ovulation-stimulating drugs (193 CC only, 29 FSH only, and 66 both). Overall, women who had used fertility drugs showed a non-statistically significantly decreased risk of breast cancer, compared with nonusers (OR = 0.82, 95% CI = 0.63 to 1.08). Women who had used fertility drugs but had not conceived a 10+ week pregnancy under treatment showed a statistically significantly decreased risk of breast cancer compared with nonusers (OR = 0.62, 95% CI = 0.43 to 0.89). Women who had used fertility drugs and conceived a 10+ week pregnancy under treatment showed a statistically significantly increased risk of breast cancer compared with unsuccessfully treated women (OR = 1.82, 95% CI = 1.10 to 3.00), although their risk was not increased compared with women who had not used fertility drugs (OR = 1.13, 95% CI = 0.78 to 1.64).
CONCLUSIONS: In the absence of a 10+ week pregnancy under treatment, exposure to ovulation-stimulating fertility drugs was associated with reduced risk of young-onset breast cancer. This apparent association was absent in women who conceived a 10+ week pregnancy under treatment, for whom risk was higher than that of unsuccessfully treated women, but similar to that of untreated women.

Hussain S, Al-Nsour F, Rice AB, Marshburn J, Yingling B, Ji Z, Zink JI, Walker NJ, Garantziotis S. Cerium dioxide nanoparticles induce apoptosis and autophagy in human peripheral blood monocytes. *ACS Nano*., 6: 5820-5829, 2012.

Cerium dioxide nanoparticles (CeO_2 NPs) have diversified industrial uses, and novel therapeutic applications are actively being pursued. There is a lack of mechanistic data concerning the effects of CeO_2 NPs on primary human cells. We aimed at characterizing the cytotoxic effects of CeO_2 NPs in human peripheral blood monocytes. CeO_2 NPs and their suspensions were thoroughly characterized, including using transmission electron microscopy (TEM), dynamic light scattering, and zeta potential analysis. Blood from healthy human volunteers was drawn through phlebotomy, and CD14+ cells were isolated. Cells were exposed to CeO_2 NPs (0.5-10 μg/mL) for 20 or 40 h, and mechanisms of cell injury were studied. TEM revealed that CeO_2 NPs are internalized by monocytes and are found either in vesicles or free in the cytoplasm. CeO_2 NP exposure leads to decrease in cell viability, and treated cells exhibit characteristic hallmarks of apoptosis (activation of Bax,

loss of mitochondrial membrane potential, DNA fragmentation). CeO_2 NP toxicity is caused by mitochondrial damage and overexpression of apoptosis inducing factor, but is not due to caspase activation or reactive oxygen species production. Moreover, CeO_2 NP exposure leads to autophagy, which is further increased after pharmacological inhibition of tumor suppressor protein p53. Inhibition of autophagy partially reverses cell death by CeO_2 NPs. It is concluded that CeO_2 NPs are toxic to primary human monocytes at relatively low doses.

Cannon RE, Peart JC, Hawkins BT, Campos CR, Miller DS. Targeting blood-brain barrier sphingolipid signaling reduces basal P-glycoprotein activity and improves drug delivery to the brain. *Proc. Natl. Acad. Sci. USA.*, 109: 15930-15935, 2012.

P-glycoprotein, an ATP-driven drug efflux pump, is a major obstacle to the delivery of small-molecule drugs across the blood-brain barrier and into the CNS. Here we test a unique signaling-based strategy to overcome this obstacle. We used a confocal microscopy-based assay with isolated rat brain capillaries to map a signaling pathway that within minutes abolishes P-glycoprotein transport activity without altering transporter protein expression or tight junction permeability. This pathway encompasses elements of proinflammatory- (TNF-α) and sphingolipid-based signaling. Critical to this pathway was signaling through sphingosine-1-phosphate receptor 1 (S1PR1). In brain capillaries, S1P acted through S1PR1 to rapidly and reversibly reduce P-glycoprotein transport activity. Sphingosine reduced transport by a sphingosine kinase-dependent mechanism. Importantly, fingolimod (FTY720), a S1P analog recently approved for treatment of multiple sclerosis, also rapidly reduced P-glycoprotein activity; similar effects were found with the active, phosphorylated metabolite (FTY720P). We validated these findings in vivo using in situ brain perfusion in rats. Administration of S1P, FTY720, or FTY729P increased brain uptake of three radiolabeled P-glycoprotein substrates, ^{3}H-verapamil (threefold increase), ^{3}H-loperamide (fivefold increase), and ^{3}H-paclitaxel (fivefold increase); blocking S1PR1 abolished this effect. Tight junctional permeability, measured as brain ^{14}C-sucrose accumulation, was not altered. Therefore, targeting signaling through S1PR1 at the blood-brain barrier with the sphingolipid-based drugs, FTY720 or FTY720P, can rapidly and reversibly reduce basal P-glycoprotein activity and thus improve delivery of small-molecule therapeutics to the brain.

Oakley RH, Revollo J, Cidlowski JA. Glucocorticoids regulate arrestin gene expression and redirect the signaling profile of G protein-coupled receptors. *Proc. Natl. Acad. Sci. USA.*, 109: 17591-17596, 2012.

G protein-coupled receptors (GPCRs) compose the largest family of cell surface receptors and are the most common target of therapeutic drugs. The nonvisual arrestins, β-arrestin-1 and β-arrestin-2, are multifunctional scaffolding proteins that play critical roles in GPCR signaling. On binding of activated GPCRs at the plasma membrane, β-arrestins terminate G protein-dependent responses (desensitization) and stimulate β-arrestin-dependent signaling pathways. Alterations in the cellular complement of β-arrestin-1 and β-arrestin-2 occur in many human diseases, and their genetic ablation in mice has severe consequences. Surprisingly, however, the factors that control β-arrestin gene expression are poorly understood. We demonstrate that glucocorticoids differentially regulate β-arrestin-1 and β-arrestin-2 gene expression in multiple cell types. Glucocorticoids act via the glucocorticoid

receptor (GR) to induce the synthesis of β-arrestin-1 and repress the expression of β-arrestin-2. Glucocorticoid-dependent regulation involves the recruitment of ligand-activated glucocorticoid receptors to conserved and functional glucocorticoid response elements in intron-1 of the β-arrestin-1 gene and intron-11 of the β-arrestin-2 gene. In human lung adenocarcinoma cells, the increased expression of β-arrestin-1 after glucocorticoid treatment impairs G protein-dependent activation of inositol phosphate signaling while enhancing β-arrestin-1-dependent stimulation of the MAPK pathway by protease activated receptor 1. These studies demonstrate that glucocorticoids redirect the signaling profile of GPCRs via alterations in β-arrestin gene expression, revealing a paradigm for cross-talk between nuclear and cell surface receptors and a mechanism by which glucocorticoids alter the clinical efficacy of GPCR-based drugs.

Wilson RH, Maruoka S, Whitehead GS, Foley JF, Flake GP, Sever ML, Zeldin DC, Kraft M, Garantziotis S, Nakano H, Cook DN. The Toll-like receptor 5 ligand flagellin promotes asthma by priming allergic responses to indoor allergens. *Nat. Med.*, 18: 1705-1710, 2012.

Allergic asthma is a complex disease characterized by eosinophilic pulmonary inflammation, mucus production and reversible airway obstruction. Exposure to indoor allergens is a risk factor for asthma, but this disease is also associated with high household levels of total and particularly Gram-negative bacteria. The ability of bacterial products to act as adjuvants suggests they might promote asthma by priming allergic sensitization to inhaled allergens. In support of this idea, house dust extracts (HDEs) can activate antigen-presenting dendritic cells (DCs) in vitro and promote allergic sensitization to inhaled innocuous proteins in vivo. It is unknown which microbial products provide most of the adjuvant activity in HDEs. A screen for adjuvant activity of microbial products revealed that the bacterial protein flagellin (FLA) stimulated strong allergic airway responses to an innocuous inhaled protein, ovalbumin (OVA). Moreover, Toll-like receptor 5 (TLR5), the mammalian receptor for FLA, was required for priming strong allergic responses to natural indoor allergens present in HDEs. In addition, individuals with asthma have higher serum levels of FLA-specific antibodies as compared to nonasthmatic individuals. Together, these findings suggest that household FLA promotes the development of allergic asthma by TLR5-dependent priming of allergic responses to indoor allergens.

Schellenberg MJ, Appel CD, Adhikari S, Robertson PD, Ramsden DA, Williams RS. Mechanism of repair of 5'-topoisomerase II-DNA adducts by mammalian tyrosyl-DNA phosphodiesterase 2. *Nat. Struct. Mol. Biol.*, 19: 1363-1371, 2012.

The topoisomerase II (topo II) DNA incision-and-ligation cycle can be poisoned (for example following treatment with cancer chemotherapeutics) to generate cytotoxic DNA double-strand breaks (DSBs) with topo II covalently conjugated to DNA. Tyrosyl-DNA phosphodiesterase 2 (Tdp2) protects genomic integrity by reversing 5'-phosphotyrosyl-linked topo II-DNA adducts. Here, X-ray structures of mouse Tdp2-DNA complexes reveal that Tdp2 β-2-helix-β DNA damage-binding 'grasp', helical 'cap' and DNA lesion-binding elements fuse to form an elongated protein-DNA conjugate substrate-interaction groove. The Tdp2 DNA-binding surface is highly tailored for engagement of 5'-adducted single-stranded DNA ends and restricts nonspecific endonucleolytic or exonucleolytic processing. Structural,

mutational and functional analyses support a single-metal ion catalytic mechanism for the exonuclease-endonuclease-phosphatase (EEP) nuclease superfamily and establish a molecular framework for targeted small-molecule blockade of Tdp2-mediated resistance to anticancer topoisomerase drugs.

BSC REVIEW OF THE BIOSTATISTICS BRANCH

The DIR Board of Scientific Counselors reviewed the Biostatistics Branch November 4-6, 2012.

Members of the Board of Scientific Counselors that Attended:

- Jack Keene, Ph.D. [BSC Chair], James B. Duke Professor, Dept. of Molecular Genetics & Microbiology, Duke University School of Medicine, Durham, NC
- Kenneth B. Adler, Ph.D., Professor, Dept. of Molecular Biomedical Sciences, College of Veterinary Medicine, North Carolina State University, Raleigh, NC
- Juan C. Celedón M.D., Dr.P.H., Neil K. Jerne Professor, Dept. of Pediatrics, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA.
- Samuel M. Cohen, M.D., Ph.D., Professor, Dept. of Pathology and Microbiology, University of Nebraska Medical Center, Omaha, NE
- Jay I. Goodman, Ph.D., Professor, Department of Pharmacology and Toxicology, Michigan State University, East Lansing, MI
- José E. Manautou, Ph.D., Associate Professor, Department of Pharmaceutical Sciences, University of Connecticut School of Pharmacy, Storrs, CT
- Roland A. Owens, Ph.D., Ex-Officio BSC Member, Assistant Director, Office of Intramural Research, NIH, Bethesda, MD

Ad Hoc Reviewers that Attended:

- Minoru S.H. Ko, M.D., Ph.D., Professor and Chair, Department of Systems Medicine, Sakaguchi Laboratory, Keio University School of Medicine, Shinanomachi, Shinjuku, Tokyo, Japan
- David Landsman, Ph.D., Senior Investigator, Chief, Computational Biology Branch, National Center for Biotechnology Information, National Library of Medicine, National Institutes of Health, Bethesda, MD
- Thomas Mathew, Ph.D., Professor, Department of Mathematics and Statistics, University of Maryland Baltimore County, Baltimore, MD
- Donald P. McDonnell, Ph.D., Glaxo-Wellcome Professor of MCB and Chairman, Department of Pharmacology and Cancer Biology, Duke University School of Medicine, Durham, NC
- Steven Self, Ph.D., Program Head, Biostatistics and Biomathematics Program, Fred Hutchinson Cancer Research Center, Seattle, WA
- Daniel O. Stram, Ph.D., Professor, Dept. of Preventive Medicine, University of Southern California, Los Angeles, CA
- Susmita Datta, Ph.D., Professor and University Scholar, Department of Bioinformatics & Biostatistics, School of Public Health and Information Sciences, University of Louisville, Louisville, KY
- Jun Liu, Ph.D., Professor, Department of Statistics, Harvard University, Cambridge, MA

Agenda:

Sunday, November 4, 2012: Doubletree Guest Suites, Closed Session

7:00 - 8:00 p.m.	Welcome and Discussion of Past Board Reviews, Drs. Linda Birnbaum, Clarice Weinberg and Darryl Zeldin
8:00 -10:00	BSC Discussion of Review, Dr. Jack Keene; BSC Chair

Monday, November 5, 2012: NIEHS Rodbell Conference Rooms 101 ABC

8:30 - 8:45 a.m.	Welcome, Drs. Birnbaum and Zeldin
8:45 - 9:05	Overview—Biostatistics Branch, Clarice R. Weinberg, Ph.D., Chief
9:05 - 9:55	Biostatistics Branch, Dmitri Zaykin, Ph.D.
9:55 - 10:45	Biostatistics Branch, Clarice R. Weinberg, Ph.D.
10:45 - 11:00	Break
11:00 - 11:50	Biostatistics Branch, Leping Li, Ph.D.
11:50 a.m.-12:35p.m.	Closed Session with Investigators, Drs. Weinberg, Zaykin and Li
12:35 - 1:30	Lunch
1:30 - 2:30	Poster Session Postdoctoral Fellows and Staff Scientists
2:30 - 2:45	Break
2:45 - 3:15	Closed Session with Fellows and Staff Scientists
3:15 - 4:05	Biostatistics Branch, Shyamal D. Peddada, Ph.D.
4:05 - 4:55	Systems Biology Group, Raja Jothi, Ph.D.
5:00 - 5:30	Closed Session with Investigators, Drs. Peddada and Jothi
5:30 - 5:45	Return to Doubletree Hotel
6:00 - 7:30	Dinner
7:30 -	Closed Session, BSC Discussion of review at Doubletree, Dr. Keene and all review team members

Tuesday, November 6, 2012: Rodbell Conference Rooms 101 ABC

8:30 - 9:30 a.m.	Closed Session – Board Debriefing To NIEHS/DIR Leadership, Dr. Keene and all review team, Members; Drs. Zeldin, Schrader and Birnbaum
9:30	Adjourn

AWARDS AND HONORS

Scientific Awards

Dr. John Cidlowski (Chief, Laboratory of Signal Transduction) is the recipient of the Allan Munck Award at Dartmouth University.

Dr. Michael Fessler (Laboratory of Respiratory Biology) received the Carol Basbaum Award from the American Thoracic Society last year. It recognizes scientific accomplishment in pulmonary research in junior faculty up through the Assistant Professor level.

Dr. Joyce Goldstein (Laboratory of Toxicology and Pharmacology) received an Honorary Tribute Dinner at the International Society for the Study of Xenobiotics meeting, Oct 18, 2011, Atlanta GA.

Dr. Harriet Kinyamu (Laboratory of Molecular Carcinogenesis) received an award for the top ranked poster at the American Association for Cancer Research annual meeting March 31-April 4, 2012, in Chicago.

Dr. Kenneth Korach (Chief, Laboratory of Reproductive and Developmental Toxicology) received the Dale Medal from the British Endocrine Society and received the Beacon Award from the Woods Hole Research Labs for advances in Frontiers in Reproduction.

Dr. Fred Miller (Acting Clinical Director, Office of Clinical Research) was named one of the Best Doctors in America.

Dr. Masa Negishi (Laboratory of Reproductive and Developmental Toxicology) was elected a Fellow of the Japanese Society of Study of Xenobiotics.

Dr. Michael Resnick (Laboratory of Molecular Genetics) was elected a Fellow of the American Association for the Advancement of Science.

Dr. Lisa Rider (Office of Clinical Research) was named an Affiliated Member, Madison's Who's Who and one of the Best Doctors in America.

Dr. John Roberts (Laboratory of Molecular Carcinogenesis) received the NIH Office of the Director Honor Award for contributions to animal care and use.

Dr. Walter Rogan (Epidemiology Branch) was elected an honorary fellow of the American Academy of Pediatrics.

Dr. Dale Sandler (Chief, Epidemiology Branch) was elected to Alpha Chapter, Delta Omega Honorary Society in Public Health, The Johns Hopkins Bloomberg School of Public Health.

Named Professorships/Lectures

Dr. Karen Adelman (Laboratory of Molecular Carcinogenesis) gave the Lester O. Krampitz Memorial Lecture, Case Western Reserve University, Dept. of Molecular Biology and Microbiology, Cleveland, OH; gave the Keynote Lecture, 21st Annual Meeting of the Medical Genetics Centre, Leiden, Holland; and was the Keynote Speaker, Leaders-in-the-Field seminar series, UCLA Jonsson Comprehensive Cancer Center, Los Angeles, CA.

Dr. David Armstrong (Laboratory of Neurobiology) was a Distinguished Lecturer, Molecular Medicine Series, Georgia State University, Atlanta, March, 2012.

Dr. Donna Baird (Epidemiology Branch) gave the Keynote Address at the 2012 Meeting of the Society for Pediatric and Perinatal Epidemiologic Research.

Dr. Lutz Birnbaumer (Laboratory of Neurobiology) gave the Keynote lecture at the joint meeting of the Physiological and Biophysical Societies of Australia and New Zealand in Sydney, Australia, December 2-5, 2012.

Dr. Thomas Kunkel (Laboratory of Molecular Genetics and Laboratory of Structural Biology) was the 2012 Keynote Speaker at the Gordon Research Conference on Mutagenesis.

Dr. Xiaoling Li (Laboratory of Signal Transduction) gave the Er Yi Innovative Lectureship, Shanghai Jiao Tong University School of Medicine, Shanghai, China. December 9, 2011.

Dr. Geoffrey Mueller (Laboratory of Structural Biology) will present the Plenary Talk at the Immunity in Cancer and Allergy PhD Program Symposium, University of Salzburg. February 4-5, 2013.

Dr. Masa Negishi (Laboratory of Reproductive and Developmental Toxicology) was the Keynote speaker at the 27th Annual Japanese Society of Study of Xenobiotics Meeting in Tokyo on November 22, 2012.

Dr. Richard Paules (Laboratory of Toxicology and Pharmacology) was the Keynote speaker at the 3rd Asian Conference on Environmental Mutagens, Hangzhou, China, October 2012.

Dr. Allen Wilcox (Epidemiology Branch) will be the 2013 Distinguished Visiting Epidemiologist, Department of Epidemiology, University of Washington, Seattle, WA.

Editorial Boards

Dr. Karen Adelman (Laboratory of Molecular Carcinogenesis) was appointed to the Editorial Board of the journal *Methods*.

Dr. David Armstrong (Laboratory of Neurobiology) was appointed to the Editorial Board of *Nature Reports*.

Dr. Douglas Bell (Laboratory of Molecular Genetics) served as the Senior Editor of the journal *Cancer Epidemiology, Biomarkers and Prevention.*

Dr. Perry Blackshear (Laboratory of Signal Transduction) was appointed to the Editorial Board of *Molecular and Cellular Biology*.

Dr. Stavros Garantziotis (Clinical Research Unit, Laboratory of Respiratory Biology) was appointed to the Editorial Board of the *American Journal of Physiology – Lung Cellular and Molecular Physiology*.

Dr. Joyce Goldstein (Laboratory of Toxicology and Pharmacology) served as a Member of the *Faculty of 1000* and served on the Editorial Boards of *Drug Metabolism and Disposition*, *Drug Metabolism Reviews* and *Frontiers in Pharmacogenetics*.

Dr. Dmitry Gordenin (Laboratory of Molecular Genetics) served on the Editorial Board of *Mutation Research - Fundamental and Molecular Mechanisms of Mutagenesis*.

Dr. Grace Kissling (Biostatistics Branch) was appointed to the Editorial Board of *Toxicologic Pathology*.

Dr. David Miller (Chief, Laboratory of Toxicology and Pharmacology) served on the Editorial Boards of: *American Journal of Physiology: Regulatory, Integrative and Comparative Physiology*, *Toxicology and Applied Pharmacology*, *Fluids and Barriers of the CNS* and *Frontiers in Pharmacology*. Dr. Miller also served as Associate Editor of the journals: *Journal of Experimental Zoology* and *Journal of Experimental Pharmacology and Therapeutics (Transport)*.

Dr. Fred Miller (Acting Clinical Director, Office of Clinical Research) served on the Editorial Board of *PLoS One*.

Dr. Lalith Perera (Laboratory of Structural Biology) was appointed to the Editorial Board of *Journal of Crystallography*.

Dr. Darryl Zeldin (Scientific Director; Laboratory of Respiratory Biology) served on the Editorial Boards of: *Journal of Biological Chemistry*, *American Journal of Physiology: Lung Cellular and Molecular Biology*, *Journal of Allergy and Clinical Immunology*, *American Journal of Respiratory Cell and Molecular Biology*, *Prostaglandins and Other Lipid Mediators*, and *Molecular and Cellular Pharmacology*.

MENTORING

Dr. Saurabh Chatterjee, a visiting fellow from the Laboratory of Toxicology and Pharmacology, will take a tenure track Assistant Professor position at South Carolina University. His mentor is Dr. Ronald Mason.

Dr. Jacqueline de Marchena, a fellow in the Laboratory of Neurobiology, was the recipient of the 2012 Catecholamine Society Travel Award. Her mentor is Dr. Patricia Jensen.

Dr. Raluca Dumitru, an IRTA fellow in the Laboratory of Molecular Carcinogenesis, completed her training and joined UNC as the Director of the Human Pluripotent Stem Cell Core Facility. Her mentor was Dr. Guang Hu.

Dr. Fumin Lin, a postdoctoral fellow in the Laboratory of Respiratory Biology, received a $1000 Travel Award for his work presented in a poster at the CRM symposium on stem cells held at the NIH campus. His mentor is Anton Jetten.

Dr. Hazel Nichols, a research fellow in the Epidemiology Branch, received a 2-year grant from the Avon Foundation ($200,000). The title of the grant is "Reproductive hormones, central adiposity, and oxidative stress in premenopausal women". She also received the "Electra Paskett Annual Scholarship Award" from the American Society for Preventive Oncology for travel to the 2013 meeting in Memphis based on the highest scoring abstract submitted by a post-doctoral fellow. Her mentor is Dr. Dale Sandler.

Dr. Anshul Pandya, a postdoctoral fellow from the Laboratory of Neurobiology, will assume a tenure-track faculty position at the University of Alaska Fairbanks campus in the state's Northwest Arctic Borough. His mentor is Dr. Jerrel Yakel.

Dr. Sabrina Robertson, a fellow in Laboratory of Neurobiology, was the recipient of the 2012 Irwin J. Kopin Travel Fellowship. Her mentor is Dr. Patricia Jensen.

Dr. Ramen Saha, a fellow in the Laboratory of Neurobiology, received a K99 award from NIMH, "Role of Histone 2A.z Isoforms in Neuronal Transcription and Synaptic Plasticity." His mentor is Dr. Serena Dudek.

Dr. Andy Seipel, a visiting fellow in the Laboratory of Neurobiology, accepted a position with Biogen in Boston. His mentor is Dr. Jerrel Yakel.