Division of Intramural Research

NAEHS Council Update

February 2009

DIR RECRUITMENTS

Investigators in Bioinformatics
The NIEHS is seeking an investigator in Bioinformatics/Computational Biology. Candidates will be considered for Senior Investigator or Tenure-Track Investigator, depending upon qualifications. The incumbent will develop and direct a strong research group to carry out independent and collaborative research in the general area of bioinformatics and computational biology, particularly as related to biological networks, analysis of high-dimensional data, proteomics, comparative and functional genomics, gene expression, and epigenetics. This work will provide a bioinformatic infrastructure and innovative data mining approaches to advance intramural research aimed at understanding biological responses to environmental stressors, in the context of cell biology, animal experimentation, clinical research and epidemiology. Dr. Thomas Kunkel, Laboratory of Molecular Genetics, is chair of the search committee. Candidates have been identified for two Tenure-Track positions.

Tenure-Track Reproductive Epidemiologist
The Epidemiology Branch, National Institute of Environmental Health Sciences, NIH, invites applications for a tenure-track epidemiologist to develop an independent investigator-initiated research program. Applicants must have an M.D. and/or Ph.D. in epidemiology or related field, at least two years of post-degree research experience, and a record of accomplishment, including relevant peer-reviewed publications. Expertise is welcome in areas of reproduction, infertility, pregnancy, child development, and early origins of later outcomes. Research on environmental and/or genetic contributors to outcomes is encouraged. Applicants will be evaluated on their demonstrated ability to conduct biologically-based, interdisciplinary, population-level research in reproductive or developmental epidemiology. Dr. E. Mitch Eddy, Laboratory of Reproductive and Developmental Toxicology, is chair of the search committee. A candidate has been identified for selection.

Staff Scientist in Membrane Signaling
The Laboratory of Neurobiology at the National Institute of Environmental Health Sciences is recruiting a staff scientist on a renewal appointment in the Membrane Signaling Group to organize electrophysiological studies of ion channel regulation by signal transduction pathways. The selectee will independently design, implement, analyze, and trouble shoot patch clamp studies of ion channel regulation and teach patch clamp electrophysiology to other members of the Membrane Signaling Group and members of other research groups within the Division of Intramural Research. Dr. Jim Putney, Laboratory of Signal Transduction, is chair of the search committee. Dr. Christian Erxleben, Laboratory of Neurobiology, NIEHS has accepted the position.

Tenure-Track X-Ray Crystallographer
The Laboratory of Structural Biology in the Division of Intramural Research of the National Institute of Environmental Health Sciences is seeking a Tenure-Track Principal Investigator in X-ray crystallography. Applicants should have a doctoral degree, a clear record of accomplishment in X-ray crystallography, and plans to develop a strong and

original research program to investigate the structure and function of proteins involved in determining biological responses to environmental stress. While applicants proposing research in all areas related to the structure of biological macromolecules will be considered, we are particularly interested in candidates proposing research plans that coincide with areas of strength in the NIEHS Intramural Program, including but not limited to signal transduction, nuclear hormone receptor signaling, epigenetics, DNA replication and repair, and pulmonary biology. Dr. Michael Resnick, Laboratory of Molecular Genetics, is chair of the search committee. Three candidates have been interviewed.

Tenure-Track Embryonic Stem Cell Biologist
The Laboratory of Molecular Carcinogenesis is recruiting a Tenure-Track Investigator - Embryonic Stem Cell Biologist with intellectual and research strengths in, but not necessarily limited to, regulation of gene expression, development, chromatin and epigenetics. The successful applicant will be expected to establish a high-quality independent research program in stem cell biology, relevant to cancer, within a group with diverse research interests and backgrounds but focused upon the molecular and environmental mechanisms of carcinogenesis. Applicants should have a Ph.D, M.D. or equivalent doctoral degree with 3 years of postdoctoral research experience, and a strong publication record. Research experience with cancer models is desirable but not mandatory. Dr. Traci Hall, Laboratory of Structural Biology, is chair of the search committee. Three candidates have been interviewed.

Tenure-Track Developmental Neurobiologist
The Laboratory of Neurobiology is recruiting a Tenure-Track Investigator to lead a high-quality independent research program on any fundamental aspect of developmental neurobiology with the potential for identifying and preventing the deleterious effects of environmental exposures on human cognitive development. Applicants should have a Ph.D., M.D., or equivalent doctoral degree with at least 3 years of postdoctoral research experience in developmental neurobiology and a strong publication record. Applicants using fluorescence imaging and genetic model organisms are particularly encouraged to apply, but the emphasis will be on identifying an outstanding scientist with an innovative research program. Dr. Jan Drake, Laboratory of Molecular Genetics, is chair of the search committee.

Tenure-Track Developmental Biologist
A position is available for a Developmental Biologist to establish an independent basic research program and form a research group in the Laboratory of Reproductive and Developmental Toxicology, Division of Intramural Research. Applications are invited from scientists with demonstrated ability for creative and productive research in cellular and molecular mechanisms of mammalian development. Of particular interest are investigators using rodent models to study cell interactions, epigenetics or other basic biomedical problems relating to the impact of the environment on development. The successful candidate will interact with investigators studying diverse problems in reproductive biology, developmental toxicology, hormone mechanisms, signal transduction, cell cycle regulation, cell growth and differentiation, apoptosis, gene

regulation, mutagenesis and DNA repair, and cancer biology. Minimum qualifications are an M.D., Ph.D., D.V.M. or equivalent doctoral degree in the biomedical sciences, at least three years of postdoctoral experience, and publications in high quality journals. Dr. Darryl Zeldin, Acting Clinical Director and Laboratory of Respiratory Biology, is chair of the search committee.

NEW APPOINTMENTS IN THE DIVISION OF INTRAMURAL RESEARCH

Dr. Raymond Tice, Chief, Biomolecular Screening Branch

Dr. Tice joined NIEHS/NTP in 2005 as the Deputy Director for the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM). In late 2008, Dr. Tice was promoted to be the Chief of the recently created NTP Biomolecular Screening Branch (BSB), which administers the NTP High Throughput Screening (HTS) program. The HTS approach will be to screen for the ability of known and suspected toxicants to interact with targets within cellular pathways critical to carcinogenicity, reproductive and developmental toxicity, genotoxicity, neurotoxicity, and immunotoxicity.

The goals of the HTS Program are to (1) prioritize substances for further in-depth toxicological evaluation (to judiciously allocate efforts and resources to maximize public health impact), (2) identify mechanisms of action for further investigation (e.g., disease-associated pathways), and (3) develop predictive models for in vivo biological response (predictive toxicology).

Through a memorandum of understanding, the NTP is partnering with the National Human Genome Research Institute's NIH Chemical Genomics Center (NCGC) and the U.S. Environmental Protection Agency's National Center for Computational Toxicology, to test a large number of compounds (~ 10,000) broadly characterizing and defining the chemical-biological space occupied by chemicals of toxicological concern in selected quantitative HTS assays at the NCGC. Data from these assays, along with full chemical characterization and assay protocol details, are being deposited into publicly accessible relational databases, such as PubChem. Secondary screens using the *Caenorhabditis elegans* model are under development at the NTP and the tripartite collaboration between the NTP, EPA, and NCGC will establish a full spectrum of secondary and tertiary screening assays to further define and characterize activities identified in initial high throughput screens.

Selected Publications

Xia M, Huang R, Witt KL, Southall N, Fostel J, Cho M-H, Jadhav A, Smith CS, Inglese J, Portier CJ, Tice RR, Austin CP. Compound cytotoxicity profiling using quantitative high-throughput screening. *Environ. Health Perspect.* 116:284-291, 2007

Kavlock RJ, Austin CP, Tice RR. Toxicity Testing in the 21st Century: Implications for Human Health Risk Assessment, *Risk Analysis* DOI: 10.1111/j.1539-6924.2008.01168.x, 2008.

Collins FS, Gray GM, Bucher JR Toxicology. Transforming environmental health protection. *Science* 319:906-907 , 2008.

Dr. Mark J. Hoenerhoff, Staff Scientist, Cellular and Molecular Pathology Branch

Dr. Mark Hoenerhoff recently joined the Cellular and Molecular Pathology Branch at NIEHS as an anatomic pathologist and Investigative Pathology Group Leader. Dr. Hoenerhoff was trained in veterinary medicine at Michigan State University, and spent three years in private practice before returning to MSU to study veterinary pathology. Following his residency in anatomic veterinary pathology, Dr. Hoenerhoff pursued PhD training at the National Cancer Institute at the National Institutes of Health. His research made significant contributions to the field of breast cancer research and stem cell biology.

Dr. Hoenerhoff's major areas of research at the NIEHS include molecular mechanisms of chemically-induced non-neoplastic and neoplastic lesions in rodent models of human disease. His research focuses on genetic mutations and epigenetic alterations resulting from exposure to various environmental contaminants and dietary supplements, leading to the development of neoplastic disease in rodents in NTP carcinogenicity bioassays. By understanding the molecular pathogenesis of cancer, oncogenic events that occur in the rodent as a result of chemical exposure can be related to changes present in the human disease, and conclusions may be made about potential human cancer risk. Another goal of these studies is to distinguish chemical-specific tumor responses from spontaneous events, and to determine if signature mutation patterns that occur in rodents following chemical exposure are similar to patterns relevant to cancer in humans

Selected Publications

Hoenerhoff MJ, Datta S, Bommi P, Sainger R, Guo W, Dimri M, Band H, Band V, Green JE, Dimri GP. Bmi-1 cooperates with H-Ras to transform human mammary epithelial cells via dysregulation of multiple growth regulatory pathways. *Cancer Res*. 67:10286-10295, 2007.

Hoenerhoff MJ, Michalowska AM, Qiu TH, Green JE. Chapter 4: Bioinformatics Approaches to the Analysis of the Transcriptome of Animal Models of Cancer, in Bioinformatics in Cancer and Cancer Therapy, G.J. Gordon, Editor. 2009, Humana Press.

Barkan D, Kleinman H, Simmons JL, Asmussen H, Kamaraju AK, Hoenerhoff MJ, Liu ZY, Costes SV, Cho EH, Lockett S, Khanna C, Chambers AF, Green JE. Inhibition of metastatic outgrowth from single dormant tumor cells by targeting the cytoskeleton. *Cancer Res.* 68:6241-6250, 2008.

Deeb KK, Michalowska AM, Yoon CY, Krummey SM, Hoenerhoff MJ, Kavanaugh C, Li MC, Demayo FJ, Linnoila I, Deng CX, Lee EY, Medina D, Shih JH, Green JE. Identification of an Integrated SV40 T/t-Antigen Cancer Signature in Aggressive Human Breast, Prostate, and Lung Carcinomas with Poor Prognosis. *Cancer Res.* 67:8065-8080, 2007.

Dr. Weichun Huang, Staff Scientist, Biostatistics Branch

Dr. Weichun Huang recently joined the Biostatistics Branch at NIEHS as a staff scientist in Bioinformatics and Biostatistics. Dr. Huang received his PhD degree in Bioinformatics-Statistics from North Carolina State University in 2005 and did his post-doctoral training at Duke University and Boston College. His research has made major

contributions to the following four areas: (1) sequence alignment algorithms for comparative genomics analysis, (2) gene regulation and regulatory DNA motif prediction, (3) conservation and turnover mechanism of transcription factor binding site in mammalian genome, and (4) applications of next-generation sequencing technologies for genetic variation detection.

At the NIEHS, Dr. Huang is focusing on supporting DIR scientists by developing and applying statistical methods and computational tools for large-scale genomics data analysis, particularly, for next-generation sequencing data analysis. The cost-effective next-generation sequencing technologies (e.g., 454, Solexa, and SOLiD) have dramatically sped up genome sequencing/re-sequencing. These new sequencing technologies not only provide a cost-effective approach for generating a deep catalog of human genetic variations, but also present a new and powerful way for studying protein-DNA interaction, gene expression, cancer mutation, genetic and epigenetic gene regulation. The vast amount of new type sequencing data produced by next-generation sequencers, however, pose formidable informatics challenges that are unmet by existing methods and tools. Dr. Huang is interested in developing novel and efficient methods and tools for identifying single-nucleotide polymorphisms (SNP), copy number variations, (CNV), and other large structure variations in the human genome. He is actively involved in the 1000 genomes project for identifying all kinds of genetic variations in the human genome. Dr. Huang is also interested in developing new statistical methods for detecting epigenetic variation with next-generation sequencing data. He is currently collaborating with biologists within and outside the institute for studying CpG methylation pattern and histone modification in the mouse and human genomes, respectively.

Selected Publications

Huang W, Marth GT. EagleView: a genome assembly viewer for next-generation sequencing technologies, *Genome Res.* 18:1538-1543, 2008

Huang W**,** Nevins JR, Ohler U., Phylogenetic simulation of promoter evolution: estimation and modeling of binding site turnover events and assessing their impact on alignment tools, *Genome Biol.* 8:R225, 2007.

Huang W, Umbach, DM Li L. Accurate anchoring alignment of divergent sequences. *Bioinformatics*, 22:29-34, 2006.

Huang W, Umbach DM, Ohler U, Li L. Optimized mixed Markov models for motif identification. *BMC Bioinformatics*, 7**:**279, 2006.

Hillier LW, Marth GT, Quinlan A, Dooling D, Fewell G, Barnett D, Fox P, JGlasscock JI, Hickenbotham M, Huang W, Magrini VJ, Richt RJ, Sander SN, Stewart DA, Stromberg M, Tsung EF, Wylie T, Schedl T, Wilson RK, Mardis ER. Whole Genome Sequencing and Variant Discovery in C. Elegans. *Nat. Methods* 5:183-188, 2008.

Dr. Keith Shockley, Staff Scientist, Biostatistics Branch

Dr. Keith Shockley recently joined the National Toxicology Program as a bioinformatics staff scientist located within the Biostatistics Branch at NIEHS. He was

trained in chemical engineering (Ph.D. 2004, North Carolina State University), where he studied thermal stress response and sugar utilization in hyperthermophilic microorganisms. At NCSU he also investigated the efficacy of continuous culture as a tool to study differential gene expression in microbial systems. Dr. Shockley expanded his interest in bioinformatics within the division of Computational and Systems Biology at The Jackson Laboratory (Bar Harbor, ME). During his postdoctoral training he described PPARγ2-mediated control of stem cell differentiation in mice and uncovered a complex transcriptional architecture in mouse chromosome substitution strains. He also collaborated to explore the molecular basis of sleep in flies and mice.

At the NIEHS, Dr. Shockley is now focusing on supporting NTP research by using genetic and environmental data to improve toxicity testing. As the availability of high-throughput data has increased, a new "systems" approach is emerging in toxicological evaluation. Notably, the Environmental Protection Agency and the National Toxicology Program have recently developed a long-range plan for toxicity testing that involves the testing of large numbers of substances. The goals of this proposal include utilizing the recent advances in molecular toxicology and bioinformatics, increasing reliance on human as opposed to animal data, and improving efficiency in design and costs. Dr. Shockley is interested in developing and applying approaches to aid these objectives. He will assist members of the National Toxicology Program and other agencies to identify genes that control biological responses to environmental exposures, analyze and interpret biological response data from high throughput screening assays, and scrutinize gene expression data from large scale microarray studies. In addition, he will use chemoinformatics to support chemical nominations and biomolecular screening, and build genetic models to predict human toxicity.

Selected Publications

Shockley KR, Lazarenko OP, Czernik PJ, Rosen CJ, Churchill GA, Lecka-Czernik B. PPAR-γ2 nuclear receptor controls multiple regulatory pathways of osteoblast differentiation from marrow mesenchymal stem cells. *J Cell Biochem* (in press).

Shockley KR, Rosen CJ, Churchill GA, Lecka-Czernik B. PPARγ2 regulates a molecular signature of marrow mesenchymal stem cells. ***PPAR Res.*** 2007:81219, 2007

Shockley KR, Churchill GA Gene expression analysis of mouse chromosome substitution strains. ***Mamm. Gen.*** 17:598-614, 2006

Shockley KR, Scott K, Pysz MA, Conners SB, Johnson MR, Montero CI, Wolfinger RD, Kelly RM. Genome-wide transcriptional variation within and between steady states for continuous growth of the hyperthermophile *Thermotoga maritima*. ***Appl. Environ. Microbiol.*** 71:5572-5576, 2005

NIEHS SCIENCE AWARDS DAY

The Sixth Annual DIR NIEHS Science Awards Day was held on November 6, 2008, at the Rall Building on the NIEHS Campus to celebrate the achievements of DIR 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 Awards Day consisted of 6 oral presentations given by fellows, students, and technicians, 68 poster presentations, oral presentations by the Scientist of the Year, Early Career Award and Outstanding Staff Scientist winners, and an Awards Ceremony. Judging for the awards was done by the NIEHS Board of Scientific Counselors, Extramural Scientists from universities in the Triangle Area, Intramural DIR Scientists and the NIEHS Training Assembly.

The following awards were presented at NIEHS Science Awards Day:

Scientist of the Year: Michael A. Resnick, Ph.D., Laboratory of Molecular Genetics
Early Career Award: Michael B. Fessler, M.D., Laboratory of Respiratory Biology
Outstanding Staff Scientist: Freya Kamel, Ph.D., Epidemiology Branch
Mentor of the Year: Ronald P. Mason, Ph.D., Laboratory of Pharmacology
Best Poster Presentation in Environmental Biology: Stephanie A. Nick McElhinny, Ph.D., Laboratory of Molecular Genetics
Best Poster Presentation in Environmental Diseases and Medicine: Paivi M. Salo, Ph.D., Laboratory of Respiratory Biology
Best Poster Presentation in Environmental Toxicology: Marcelo G. Bonini, Ph.D., Laboratory of Pharmacology
Best Oral Presentation: Daniel A. Gilchrist, Ph.D., Laboratory of Molecular Carcinogenesis
Paper of the Year, From the Laboratory of Molecular Genetics: F. Storici, K. Bebenek, T.A. Kunkel, D.A. Gordenin and M.A. Resnick. “RNA-templated DNA Repair” Nature 447: 338-341, 2007

TRAINING AND MENTORING

The NIH Pathway to Independence Award (K99/R00)

The Pathway to Independence (PI) Award Program is designed to facilitate receiving an R01 award earlier in an investigator's research career. The primary, long-term goal of the PI Award Program is to increase and maintain a strong cohort of new and talented, NIH-supported independent investigators. The PI Award will provide up to five years of support consisting of two phases. The initial phase will provide 1-2 years of mentored support for highly promising, postdoctoral research scientists. This phase will be followed by up to 3 years of independent support contingent on securing an independent research position. Award recipients will be expected to compete successfully for independent R01 support from the NIH during the career transition award period. The PI Award is limited to postdoctoral trainees who propose research relevant to the mission of one or more of the participating NIH Institutes and Centers.

> Arno G. Siraki, Ph.D., received the K99/R00 grant for his proposal entitled, "Mechanisms of aniline-induced agranulocytosis." Dr. Siraki will train in the Laboratory of Pharmacology and Chemistry under the mentorship Dr. Ronald P. Mason.

ST*AR Award from the American Academy of Allergy, Asthma and Immunology

Cindy Visness and Michelle Sever, two graduate students from the Laboratory of Respiratory Biology, received ST*AR Awards from the American Academy of Allergy, Asthma and Immunology. Their mentor is Dr. Darryl Zeldin (Acting Clinical Director, Laboratory of Respiratory Biology).

The North Carolina Society of Toxicology President's Postdoctoral Award for Research

Erik Tokar, Ph.D. was the first place winner for his study entitled "Stem cell selection facilitates arsenic-induced malignant transformation via innate resistance, hyper-adaptability and over-production." His mentor is Dr. Michael Waalkes (Environmental Toxicology Program, NCI at NIEHS).

Scott Auerbach, Ph.D., was the second place winner for his study entitled "Prediction of hepatocarcinogenic potential in male rats using machine learning methods informed by genome-wide expression analysis." His mentor is Dr. Richard Irwin (Toxicology Branch).

TOP DIR PAPERS FOR THE YEAR 2008

Stimulus-Responsive Genes are Marked for Activation

NIEHS investigators found that many genes involved in the *Drosophila* innate immune response and other stimulus-response pathways are poised for activation. These genes recruit the RNA polymerase to the promoter before activation, but the progress of the RNA polymerase into the gene is blocked prior to receipt of an activating signal. In addition to the kinetic advantage afforded by pre-loading the RNA polymerase enzyme on a given gene, a novel function for the RNA polymerase stalled near these gene promoters was uncovered: to block the assembly of repressive chromatin structures. In this way, the presence of a poised RNA polymerase near the promoters of inactive stimulus-responsive genes maintains them in an "activate-able" state, by which the promoter is kept free of nucleosomes and accessible to upstream activators and additional RNA polymerase molecules. These results explain how rapid up-regulation of gene expression occurs in response to specific signals from the environment (e.g. stress and/or immune challenge).

Gilchrist DA, Nechaev S, Lee C, Gosh SKB, Collins J, Li L, Gilmour DS, Adelman K. NELF-mediated stalling of Pol II can enhance gene expression by blocking promoter-proximal nucleosome assembly. *Genes Dev.* 22:1921-1933, 2008.

How Double Helical DNA Is Replicated.

The two DNA strands are oriented anti-parallel to each other yet DNA replication only proceeds in one direction. These two facts require that one DNA strand of the double helix be replicated first by a so-called "leading strand" polymerase, followed slightly thereafter by replication of the other strand by a "lagging strand" polymerase. Amazingly, 54 years after Watson and Crick's description of the DNA double helix, the identity of the polymerases in higher organisms that replicate the leading and lagging strands has remained uncertain. That situation recently changed when, in collaboration with investigators at Washington University in St. Louis, NIEHS scientists published a study indicating that, in the model eukaryote budding yeast, the lagging strand is replicated by DNA polymerase delta. The knowledge that DNA polymerase delta replicates the lagging strand advances our fundamental understanding of how the genome is replicated, and it also places us one step closer to understanding the origins of genome instability that underlie diseases in humans whose occurrence is influenced by the environment.

Nick McElhinny SA, Gordenin DA, Stith CM, Burgers PMJ, Kunkel TA. Division of labor at the eukaryotic replication fork. *Mol. Cell* 30:137-144, 2008.

RNA Recognition Properties of PUF Proteins Can be Adapted by Simple Substitutions

Researchers at the NIEHS determined the three-dimensional atomic structures of a yeast protein, Puf4p, which regulates target messenger RNA stability. These structural studies along with biochemical experiments revealed that the protein binds to its target RNAs with a required 'spacer' nucleotide flipped away from the RNA binding surface. Introduction of two amino acid residue changes reversed the RNA recognition specificity so that the spacer nucleotide is no longer required. Appropriate regulation of target mRNA expression by PUF proteins is critical for maintenance of stem cell maintenance and embryonic development stem cells in humans and other organisms Structural and biochemical studies of yeast PUF4 protein revealed how this family of proteins is adapted to recognize specific, diverse mRNA sequences. This knowledge can be exploited for design of PUF proteins for therapeutic or experimental purposes, such as the development of artificial splicing factors to modulate disease-related defects in pre-mRNA splicing.

Miller MT, Higgin JJ, Hall TMT, Basis of altered RNA-binding specificity by PUF proteins revealed by crystal structures of yeast Puf4p. *Nat. Struct. Mol. Biol.* 14:397-402, 2008.

Structures of DNA Polymerase β Provide the First Glimpse of Pre-Mutagenic DNA Synthesis

Researchers at NIEHS used crystallographic structures of DNA polymerase β (Pol β) with right (matched) and wrong (mismatched) nucleotide substrates to gain insight on how mutations are averted during the enzymatic process of DNA synthesis. The team created G-A and C-A mismatches in the Pol β active site by employing a stable nucleotide analog, dAMPCPP, which could bind to the polymerase but not be inserted. Surprisingly, the structures revealed that both types of substrates (matched and mismatched) produced the same polymerase conformation. However, the mismatched substrate induced a shift in the template strand that produced an abasic site-like pre-synthesis intermediate. The structures are consistent with mutagenesis studies and provide a strategy to avert misinsertion of the wrong nucleotide. This study sheds light on the specific structural changes necessary during high fidelity DNA synthesis, a process central to DNA repair and replication and, ultimately, to protection against mutations due to environmental exposures.

Batra VK, Beard WA, Shock DD, Pedersen LC, Wilson SH. Structures of DNA polymerase beta with active site mismatches suggest a transient abasic site intermediate during misincorporation. *Mol. Cell* 30:315-324, 2008.

Diabetes Risk Associated with Pesticide Use

Pesticide applicators who used chlorinated pesticides on more than 100 days in their lifetime were found to be at greater risk of developing diabetes. NIEHS investigators studied the incidence of diabetes in the Agricultural Health Study, a prospective study of

31,787 licensed pesticide applicators. Since enrollment, 1,171 applicators reported a new diagnosis of diabetes. Among the 50 different pesticides studied, diabetes risk was increased with both ever use and increasing days of use of seven specific pesticides -- aldrin, chlordane, heptachlor, dichlorvos, trichlorfon, alachlor and cynazine. The strongest relationship was found for trichlorfon, with an 85 percent increase in risk for frequent and infrequent users and nearly a 250 percent increase for those who used it more than 10 times. This is one of the largest studies looking at the potential effects of pesticides on diabetes incidence in adults. The results suggest that pesticides may be a contributing factor for diabetes along with known risk factors such as obesity, lack of exercise and having a family history of diabetes. Although the amount of diabetes explained by pesticides is small, these new findings may extend beyond the pesticide applicators in the study. Some of the pesticides used by these workers are used by the general population, though the strength and formulation may vary. Other insecticides in this study are no longer available on the market; however, these chemicals persist in the environment and measurable levels may still be detectable in the general population and in food products.

Montgomery MP, Kamel F, Saldana TM, Alavanja MCR, Sandler DP. Incident diabetes and pesticide exposure among licensed pesticide applicators: Agricultural Health Study 1993 – 2003. *Am. J. Epidemiol*. 167:1235-1246, 2008.

An expanded biological repertoire for Inositol(3,4,5,6)-tetraphosphate through its modulation of ClC-3 function.

Inositol phosphates are “second messengers” that can play key roles in helping cells adapt to environmental insults, toxins, infections, or genetic defects. Inositol(3,4,5,6)-tetraphosphate (Ins(3,4,5,6)P(4)) inhibits plasma membrane chloride ion flux in secretory epithelia. However, in most other mammalian cells, receptor-dependent elevation of Ins(3,4,5,6)P(4) levels is an "orphan" response that lacks biological significance. NIEHS scientists have shown that the chloride ion channel, ClC-3, is inhibited by Ins(3,4,5,6)P4, thus defining a signal transduction pathway involving Ins(3,4,5,6)P4. They have also expanded the range of cell types that respond to Ins(3,4,5,6)P4 by showing that Ins(3,4,5,6)P(4) inhibits the ClC-3 conductance in postsynaptic membranes of neonatal hippocampal neurons. This signal transduction pathway could be involved in other cellular processes in which ClC-3 function may be regulated by Ins(3,4,5,6)P4 including tumor cell migration, apoptosis, and inflammatory responses, suggesting that Ins(3,4,5,6)P4 is a ubiquitous cellular signal with diverse biological actions.

Mitchell J, Wang X, Zhang G, Gentzsch M, Nelson DJ, Shears SB. An Expanded Biological Repertoire for Ins(3,4,5,6)P4 through its Modulation of ClC-3 Function *Curr. Biol.* 18:1600-1605, 2008.

DEPs Involved in a Novel Blood-Brain Barrier Signaling Pathway

Scientists from NIEHS have shown that diesel exhaust particles alter blood-brain barrier function through oxidative stress and proinflammatory cytokine production. Diesel exhaust particles are the main particulate component of urban air pollution worldwide. When brain capillaries isolated from rats are exposed to diesel exhaust particles, a signaling pathway involving NADPH oxidase and tumor necrosis factor alpha was activated, resulting in increased expression of P-glycoprotein, a major blood-brain barrier transporter. The results reveal a novel blood-brain barrier signaling pathway activated by urban air pollutants that could affect pharmacotherapy for a number of CNS diseases.

Hartz AM, Bauer B, Block ML, Hong JS, Miller DS. Diesel exhaust particles induce oxidative stress, proinflammatory signaling, and P-glycoprotein up-regulation at the blood-brain barrier. *FASEB J.* 22: 2723-2733, 2008

Neuronal Activity Reshapes Brain Circuitry

During postnatal development, connections between neurons, or synapses, are formed in abundance and then eliminated to shape the brain circuitry according to experience. NIEHS researchers discovered that continued weakening of synapses, induced with prolonged low-frequency stimulation, can lead to loss of synapses. Small synapses were found to be most susceptible to loss. This finding represents the first step in uncovering the mechanisms responsible for such activity-dependent synapse elimination, which likely plays an important role in developmental disorders such as schizophrenia and autism.

Bastrikova N, Gardner GA, Reece JM, Jeromin A, Dudek SM. Synapse elimination accompanies functional plasticity in hippocampal neurons. *Proc. Natl. Acad. Sci. USA.* 105:3123-3127, 2008

The Human ERG1 Channel Polymorphism, K897T, Creates a Phosphorylation Site That Inhibits Channel Activity

Polymorphisms in the human ether-a-go-go-related gene 1, hERG1, are associated with cardiac arrhythmias. The Kv11.1 channels encoded by hERG1 are also essential for rhythmic excitability of the pituitary, where they are regulated by thyroid hormone through a signal transduction cascade involving the phosphatidylinositol 3-kinase (PI3K) and the Ser/Thr-directed protein phosphatase, PP5. NIEHS investigators showed that the hERG1 polymorphism at codon 897, which is read as a Thr instead of a Lys, creates a new phosphorylation site for the Akt protein kinase on the Kv11.1 channel protein. Consequently hormonal signaling through the PI3K signaling cascade, which normally stimulates the K897 channels through PP5-mediated dephosphorylation, inhibits the T897 channels through Akt-mediated phosphorylation. Thus, hormonal regulation of Kv11.1 in humans with the K897T polymorphism is predicted to prolong the QT interval of cardiac myocytes. A systematic bioinformatics search for single nucleotide polymorphisms in human ion channel genes identified fifteen additional candidates for such "phosphorylopathies," which are predicted to create or destroy putative phosphorylation sites. Thus, changes in protein phosphorylation might represent a general mechanism for the effects of genetic variation on human health and its interaction with the environment.

Gentile S, Martin N, Scappini E, Williams J, Erxleben C, Armstrong DL. The human ERG1 channel polymorphism, K897T, creates a phosphorylation site that inhibits channel activity. *Proc. Natl. Acad. Sci. USA.* 105:14704-14708, 2008.

NOS and Nitroglycerin-Mediated Vasodilation

Nitroglycerin helps patients with angina and a past history of heart attacks by relaxing the smooth muscles around blood vessels, allowing more blood to reach cardiac muscles, but the exact mechanism involved in nitric oxide synthase (NOS) activation was unknown. Researchers at NIEHS and the University of Sao Paulo School of Medicine have found evidence that nitroglycerin triggered constitutive NOS activation using cell cultures, isolated vessels, and whole animals. The work may offer insight into the molecular mechanisms involved in nitrate resistance. The team's studies indicated that endothelial NOS was phosphorylated at Ser1177 on the endothelial isoform and Ser852 on the neuronal isoform in the aortae of mice and rats treated with nitroglycerin, which confirmed that isoforms of NOS were involved in vasorelaxation. Aortic ring studies determined that high doses of nitroglycerin produced vasodilation that was independent of the endothelium and could not be annulled by NOS inhibitors. At higher doses nitroglycerin is known to be bioactivated to nitric oxide.

Bonini MG, Stadler K, Silva Sde O, Corbett J, Dore M, Petranka J, Fernandes DC, Tanaka LY, Duma D, Laurindo FR, Mason RP. Constitutive nitric oxide synthase activation is a significant route for nitroglycerin-mediated vasodilation. *Proc. Natl. Acad. Sci. USA.* 105:8569-8574, 2008.

AWARDS AND HONORS

Dr. Trevor K. Archer (Chief, Laboratory of Molecular Carcinogenesis) served on the Editorial Board of the *Journal of Biological Chemistry*.

Dr. Donna Baird (Epidemiology Branch) was the Raymond Pearl Memorial Lecturer at the 2008 annual meeting of the Human Biology Association and was named Associate Editor of the *American Journal of Epidemiology.*

Dr. Jack Bishop (Toxicology Branch) received the Environmental Mutagen Society Appreciation Award for Exemplary and Dedicated Service to the Society as Treasurer.

Dr. John Cidlowski (Chief, Laboratory of Signal Transduction) received the Edwin B. Astwood Award from the Endocrine Society in 2008.

Dr. William Copeland (Laboratory of Molecular Genetics) was appointed to the Editorial Board of the *Journal of Biological Chemistry.*

Dr. Greg Dinse (Biostatistics Branch) was appointed to the Editorial Board of the journal *Lifetime Data Analysis.*

Dr. E. Mitch Eddy (Laboratory of Reproductive and Developmental Toxicology) served as Associate Editor of *Biology of Reproduction*; was on the Executive Council of The Society for the Study of Reproduction and; was the Chair of the North American Testis Workshop.

Dr. Dori Germolec (Toxicology Branch) was elected to serve on the Education Committee for the Society of Toxicology.

Dr. Joyce Goldstein (Laboratory of Pharmacology) served on the Editorial Boards of *Drug Metabolism and Deposition* and *Drug Metabolism Reviews.*

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

Dr. Traci Hall (Laboratory of Structural Biology) was named to the American Society for Biochemistry and Molecular Biology Meetings Oversight Committee.

Dr. Anton Jetten (Laboratory of Respiratory Biology) served on the Editorial Boards of *Molecular and Cellular Biology*, the *Journal of Biomedicine and Biotechnology* and the *International Journal of Cell Biology*.

Dr. Maria B. Kadiiska (Laboratory of Pharmacology) received the "Free Radical Biology & Medicine Top most cited papers 2005 - 2007 Award" from Elsevier Publishers at the 15th Annual Meeting of the Society for Free Radical Biology and Medicine for her paper "Biomarkers of Oxidative Stress Study II. Are oxidation products of lipids, proteins, and DNA markers of CCl4 poisoning?" *Free Radic Biol Med* 38: 711-718, 2005.

Dr. Steven Kleeberger (Chief, Laboratory of Respiratory Biology) was the keynote speaker at the Society of Toxicology Symposium "Host susceptibility and chemical safety testing: new approaches to estimate risks in the human population" and at the Gordon Conference on "Mechanisms of Toxicity". Dr. Kleeberger also served on the EPA Scientific Advisory Board on Particulate Matter (PM) Research Centers Program as well as a panelist on the EPA Ozone National Ambient Air Quality Standards Review Workshop.

Dr. Thomas Kunkel (Laboratory of Molecular Genetics; Chief Laboratory of Structural Biology) was the Keynote Speaker at the Workshop on AID Biology and Its Role

in Human Disease and was the Distinguished "Beach Lecturer" at Perdue University.

Dr. Frederick W. Miller (Office of Clinical Research) was elected to the Editorial Board of *The Open Rheumatology Journal.*

Dr. Pierre Bushel (Biostatistics Branch) was awarded a Yerby fellowship as an Assistant Professor of Bioinformatics at the Harvard School of Public Health, Harvard University with dual appointments in the Department of Biostatistics and Department of Environmental Health.

Dr. David Resnik (Office of the Scientific Director) served as Book Review Editor for *Policy Studies in Ethics, Law, and Technology* and was on the Editorial Boards of *The Open Clinical Trails Journal* and *Environmental Health Insights.*

Dr. Lisa Rider (Office of Clinical Research) was invited to serve on the Editorial Board of *The Open Rheumatology Journal.*

Dr. Robert Sills (Chief, Cellular and Molecular Pathology Branch) served as the Associate Editor of the Environmental Pathobiology Section of *Veterinary Pathology*.

Dr. William Stokes (National Toxicology Program Operation Branch) received the 2008 James A. McCallam Award from the Association of Military Surgeons; the Karl F. Meyer-James H. Steele Gold Head Cane Award from the American Veterinary Medical Association and; the Field Medical Readiness Badge from the U.S. Public Health Service.

Dr. Nigel Walker (National Toxicology Program Operation Branch) was appointed to the Editorial Boards of *Environmental Health Perspectives* and *Toxicology and Applied Pharmacology*.

Dr. Allen Wilcox (Epidemiology Branch) received an honorary doctorate from the University of Bergen, Norway.

Dr. Samuel Wilson (Deputy Director and Laboratory of Structural Biology) was elected a fellow of the American Association for the Advancement of Science.

Dr. Jerrel Yakel (Laboratory of Neurobiology) was elected a fellow of the American Association for the Advancement of Science.

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