Division of Intramural Research

NAEHS Council Update

February 2011

DIR RECRUITMENTS

Director Division of Intramural Research
The NIEHS is seeking an exceptional scientific leader interested in being a part of a dynamic management team to fill the position of Director, Division of Intramural Research. In addition, the selectee will also serve as the Scientific Director. The incumbent of this position will direct laboratory and clinical research. The Director, DIR, also serves as a principal advisor to the Institute Director on intramural scientific activities involving interdisciplinary biomedical research programs; develops and recommends policies for the execution of research programs; determines effectiveness of current programs and recommends policies for new programs; and develops new and revised programs to meet national environmental health needs. The Division is organized into five scientific programs, including the Clinical Research Program, which highlight the areas of research excellence of NIEHS. These programs are highly interrelated, interactive and synergistic. Using the interdisciplinary biomedical research approach, the mission of the DIR is to contribute to the basic understanding of biological and chemical processes, understanding of the contributions of environmental agents to human disease and dysfunction and to the underlying mechanisms of environmentally associated diseases. Dr. Patricia Grady, Director, National Institute of Nursing Research, is chair of the search committee.

Staff Scientist, Veterinarian, Comparative Medicine Branch
The NIEHS is recruiting for a Staff Scientist who will serve as a veterinarian in the Comparative Medicine Branch. The Comparative Medicine Branch (CMB) provides core services that include full veterinary diagnostic and surgical services, rederivation of rodent lines, embryo cryopreservation, radiographic, ultrasonic and bioluminescence imaging, and behavioral phenotyping. The Branch advises Institute scientists of appropriate animal models for use in Institute research programs, provides support for the Institute's Animal Care and Use Committee, maintains collaborative laboratories in microbiology, experimental surgery and laboratory animal medicine, and plans and conducts research appropriate to these laboratory functions. The responsibilities of this position require the applicant to hold a DVM/VMD from an AVMA-accredited or approved college, a current license to practice veterinary medicine in any state in the United States, board certification in laboratory animal medicine, and excellent interpersonal skills. Expertise and experience should include interaction and cooperation with scientific staff in a manner that promotes and facilitates their scientific programs. Experience training or teaching laboratory animal medicine residents is desirable. In addition to a DVM/VMD, a Ph.D. in a discipline related to CMB support services and laboratories such as but not limited to pathology, microbiology, biology, anatomy, genetics, etc., is desirable. The staff scientist will assist the animal care program in maintaining the highest standards and AAALAC accreditation, provide professional support to the research efforts of all Division of Intramural Research scientists using animals, and assure the continued growth of the large and complex CMB core services (previously listed) in the animal care program. Staff scientist positions within the NIH system are equivalent to research assistant professor positions in academia. Dr. John Roberts (Laboratory of Molecular Carcinogenesis) is chair of the search committee. A candidate has been identified.

NEW APPOINTMENTS IN THE DIVISION OF INTRAMURAL RESEARCH

Dr. Humphrey Hung-Chang Yao
Reproductive Developmental Biology Group
Laboratory of Reproductive and Developmental Toxicology

Dr. Humphrey Yao recently joined the Laboratory of Reproductive and Developmental Toxicology at NIEHS as a tenure-track principal investigator. Dr. Yao received his doctoral degree at the University of Illinois in Urbana-Champaign in 1999 and then completed his postdoctoral training at Duke University Medical Center in 2002. He became Assistant Professor in the Department of Comparative Biosciences at University of Illinois in Urbana-Champaign in 2003 and received tenure in 2009. Dr. Yao moved to NIEHS on August 9, 2010.

Compelling animal evidence and human epidemiological data have revealed that impairment of fetal organ development has profound consequences on adult health. The concept of "fetal origins of adult diseases" also applies to the reproductive systems where formation of most reproductive organs is completed before birth. Defects in reproductive organ formation manifest as birth defects in severe cases (i.e. pseudohermaphroditism). However, minor abnormalities are often left undetected and become a potential cause of fertility problems and neoplasia when the affected individual reaches adulthood. The mission of Dr. Yao's group is to understand the basic process of organ formation as well as the potential implication on impacts of endocrine disruptor exposure to gonad development in fetuses and fertility in adulthood. The current research interests include: 1) Understand how different somatic cell lineages (Sertoli and Leydig cells in the testis and granulosa and theca cells in the ovary) are established in the fetal testis and ovary, respectively; 2) Define the cellular processes that lead to formation of testis architecture and follicle assembly in the ovary; and 3) Investigate the effects of in utero exposure to endocrine disruptors on gonad organogenesis and lingering impacts on fertility in adulthood.

Selected Publications

Archambeault DR, Yao HH. Activin A, a product of fetal Leydig cells, is a unique paracrine regulator of Sertoli cell proliferation and fetal testis cord expansion. *Proc. Natl. Acad. Sci. U.S.A.*, 107:10526-10531, 2010.

Liu CF, Parker K, Yao HH. WNT4/beta-catenin pathway maintains female germ cell survival by inhibiting activin betaB in the mouse fetal ovary. *PLoS One,* 5:e10382, 2010.

Huang CC, Miyagawa S, Matsumaru D, Parker KL, Yao HH. Progenitor cell expansion and organ size of mouse adrenal is regulated by sonic hedgehog. *Endocrinology*, 151:1119-1128, 2010.

Gupta RK, Singh JM, Leslie TC, Meachum S, Flaws JA, Yao HH. Di-(2-ethylhexyl) phthalate and mono-(2-ethylhexyl) phthalate inhibit growth and reduce estradiol levels of antral follicles in vitro. *Toxicol. Appl. Pharmacol*., 242:224-230, 2010.

Dr. Richard Kwok
Epidemiology Branch

Dr. Richard Kwok recently joined the Epidemiology Branch at NIEHS as a staff scientist. Dr. Kwok trained in environmental chemistry (BSPH, UNC-Chapel Hill) and epidemiology

(MSPH; PhD, UNC-Chapel Hill). His research has made major contributions in two different areas: (1) the understanding of how drinking water arsenic affects cardiovascular disease in pregnant women in Inner Mongolia, China and 2) UV Dosimetry and skin cancer risk. He has worked on cross study analyses of environmental causes of childhood disease using data from prospective children's cohort studies such as the National Children's Study and the Norwegian Mother and Child Cohort Study through the International Childhood Cancer Cohort Consortium. Additionally, he is interested in developing models to inform climate change adaptation efforts.

At the NIEHS, Dr. Kwok is focusing on the Gulf Long-term Follow-up (GuLF) Study, which will investigate potential health effects associated with clean-up activities following the Deepwater Horizon disaster in the Gulf of Mexico. The long-term human health consequences of oil spills are largely unknown. Exposures range from negligible to potentially significant, especially for those doing tasks involving direct exposure to crude or burning oil, or dispersants. Heat and stress experienced by workers may also have adverse consequences. In addition, the widespread economic and lifestyle disruption caused by the spill may contribute to mental health problems among subsets of the population. Dr. Kwok is interested in developing exposure models for these tasks and investigating potential associations to adverse health outcomes.

Selected Publications

Kwok RK, Mendola P, Liu ZY, Savitz DA, Heiss G, He LL, Xia Y, Lobdell D, Zeng D, Thorp JM Jr, Creason JP, Mumford JL. Drinking water arsenic exposure and blood pressure in healthy women of reproductive age in inner Mongolia, China. *Toxicol. Appl. Pharmacol.,* 222:337–343, 2007.

Yu CL, Li Y, Freedman DM, Fears T, Kwok RK, Chodick G, Alexander BH, Kimlin M, Kricker A, Armstrong BK, Linet MS. Assessment of lifetime cumulative sun exposure using a self-administered questionnaire: Reliability of two approaches. *Cancer Epidemiol. Biomark. Prevent*., 18:464-471, 2009.

Mumford J, Wu K, Xia Y, Kwok RK, Yang Z, Foster J, Sanders WE Jr. Chronic arsenic exposure and cardiac repolarization abnormalities with qt interval prolongation in a population-based study. *Environ. Health Perspect.,* 115:690–694, 2007.

Kwok RK. A review and rationale for studying the cardiovascular effects of drinking water arsenic in women of reproductive age. *Toxicol. Appl. Pharmacol.,* 222: 344–350, 2007.

Kwok RK, Linet MS, Chodick G, Kleinerman RA, Freedman DM, Fears T, Johnson RE, Alexander BH. Simplified categorization of outdoor activities for male and female U.S. indoor workers; application to ultraviolet radiation assessment questionnaires. *Photochem. Photobiol.*, 85;45-49, 2009.

Dr. Irene Whitt
Environmental Autoimmunity Group
Office of Clinical Research

Dr. Irene Whitt recently joined Drs. Fred Miller and Lisa Rider as a Staff Clinician in the Environmental Autoimmunity Group at NIEHS, NIH Bethesda Campus. Dr. Whitt received her MD degree from Vanderbilt University Medical School and completed a residency in Internal Medicine at the Mayo Clinic. She worked for 1 year in private practice before returning to the Mayo Clinic to pursue a fellowship in Rheumatology, which she completed in June 2010, before

joining EAG. She has had broad and varied research interests throughout her medical training, but her recent contribution to rheumatology research has been in beginning to understand cardiovascular risk and heart disease in patients with idiopathic inflammatory myopathies.

At NIEHS, Dr. Whitt is involved in a wide spectrum of research, focusing on several areas: 1) analyzing results from an NHANES study assessing the prevalence of antinuclear antibodies and associations with xenobiotic exposure, 2) investigating mortality in patients with inflammatory myositis, 3) assisting with data collection for an international study to develop new classification criteria for the inflammatory myopathies, 4) starting a new clinical protocol at the Bethesda campus studying environmental risk factors for developing the antisynthetase syndrome in patients with myositis, and 5) investigating the potential clinical and research utility of various imaging techniques (CT and MRI) for the diagnosis and follow up of patients with myositis.

Selected Publications:

Whitt I, Miller F. "Inflammatory Myopathies: Polymyositis, Dermatomyosits, and Related Conditions", in *Primary Care Rheumatology*, Lippincott. In press.

Whitt I, Crowson C, Ytterberg S. High Burden of Cardiovascular Risk in Patients with Inflammatory Myositis. (submitted)

DIR RESEARCH UPDATE

New Insights into Regulating Synaptic Plasticity: Implications for Autism and Schizophrenia

Serena M. Dudek, Ph.D., Senior Investigator

Synaptic and Developmental Plasticity Group
Laboratory of Neurobiology, DIR, NIEHS

Humans have a remarkable ability to learn from their environment after birth, but this plasticity also makes them susceptible to environmental toxicants. Accordingly, disruption of brain development can have lifelong consequences on brain circuitry and thus cognitive potential. At the cellular level learning is accomplished by changing the strength of the synaptic connections between neurons. Therefore, we are working to identify the underlying molecular processes of synaptic plasticity during postnatal development. Using molecular biological techniques, patch clamp recordings and confocal microscopic imaging from neurons in brain slices and dissociated culture, we ask how neuronal activity controls gene transcription and brain circuitry and what molecular processes determine why some brain regions are more plastic than others during development and in adulthood. During the past several years we have made three important advances: 1) We have identified a molecular mechanism for rapidly turning on transcription in response to neuronal activity; 2) We have developed a model in which we can observe activity-dependent synapse pruning in living slices of rat brain; and 3) We have discovered that neurons in adjacent regions of the hippocampus, a brain structure with a prominent role in memory, have very different capacities for plasticity, and we have begun to identify the molecular bases for these differences. Specifically, we have discovered that CA2 neurons have a particularly robust ability to extrude intracellular calcium, which is required for synaptic plasticity. Related to this last project, we found that neurons in area CA2 are primary targets of caffeine and neuropeptides important for social behaviors of the kind that are disrupted in the autism spectrum disorders. These findings are likely to shed light on environmental causes of psychiatric diseases such as schizophrenia and autism.

NIEHS SCIENCE AWARDS DAY

The Eighth Annual DIR NIEHS Science Awards Day was held on November 4, 2010, 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 9 oral presentations given by fellows, students, and technicians, 94 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 Trainees Assembly.

The following awards were presented at NIEHS Science Awards Day:

Scientist of the Year: Dale P. Sandler, Ph.D., Epidemiology Branch

Early Career Award: Xiaoling Li, Ph.D., Laboratory of Signal Transduction

Outstanding Staff Scientist: Jane A. Hoppin, Sc.D., Epidemiology Branch

Mentor of the Year: Matthew J. Longley, Ph.D., Laboratory of Molecular Genetics

Best Poster Presentation in Environmental Biology: Deepti Dwivedi, Ph.D., Laboratory of Molecular Genetics, "Novel Mutator Mutants of E. coli NrdAB Ribonucleotide Reductase: Alterations at Allosteric Regulatory Sites and Correlation with in vivo dNTP Pools"

Best Poster Presentation in Environmental Diseases and Medicine: Ginger W. Muse, Laboratory of Molecular Carcinogenesis, "RNA Pol II Pausing Plays a Critical Role in the Mammalian Inflammatory Response"

Best Poster Presentation in Environmental Toxicology: Kalina Ranguelova, Ph.D., Laboratory of Toxicology and Pharmacology, "Formation of Highly Reactive Sulfite-Derived Free Radicals by the Activation of Human Neutrophils"

Best Oral Presentation: Jason P. Stanko, Ph.D., Cellular and Molecular Pathology Branch, **"**A Comparison of Mammary Gland Developmental Delays and DMBA-induced Mammary Tumorigenesis in Long-Evans and Sprague Dawley Rat Offspring Prenatally Exposed to Atrazine"

Paper of the Year: From the Laboratory of Signal Transduction: A. Purushotham, T.T. Schug, Q. Xu, S. Surapureddi, X. Guo and X. Li. "Hepatocyte-Specific Deletion of SIRT1 Alters Fatty Acid Metabolism and Results in Hepatic Steatosis and Inflammation" Cell Metabolism 9: 327-338, 2009.

TOP DIR PAPERS PUBLISHED IN 2010

Acetaminophen-Induced Transcriptional Changes Predict Liver Injury in Humans

Summary: A collaborative research effort led by NIEHS scientists demonstrated that non-toxic doses of acetaminophen induce transcriptional changes in humans similar to those observed in rats exposed to toxic doses of the drug. These findings reveal potential biomarkers that may indicate early signs of drug-induced liver injury (DILI).

Abstract: The diagnosis and management of drug-induced liver injury (DILI) is hindered by the limited utility of traditional clinical chemistries. It has recently been shown that hepatotoxicants can produce compound-specific changes in the peripheral blood (PB) transcriptome in rodents, suggesting that the blood transcriptome might provide new biomarkers of DILI. To investigate in humans, we used DNA microarrays as well as serum metabolomic methods to characterize changes in the transcriptome and metabolome in serial PB samples obtained from six healthy adults treated with a 4-g bolus dose of acetaminophen (APAP) and from three receiving placebo. Treatment did not cause liver injury as assessed by traditional liver chemistries. However, 48 hours after exposure, treated subjects showed marked down-regulation of genes involved in oxidative phosphorylation/mitochondrial function that was not observed in the placebos ($P < 1.66E-19$). The magnitude of down-regulation was positively correlated with the percent of APAP converted to the reactive metabolite *N*-acetyl-*p*-benzoquinone-imide (NAPQI) ($r= 0.739$; $P= 0.058$). In addition, unbiased analysis of the serum metabolome revealed an increase in serum lactate from 24 to 72 hours postdosing in the treated subjects alone ($P< 0.005$). Similar PB transcriptome changes were observed in human overdose patients and rats receiving toxic doses. Conclusion: The single 4-g APAP dose produced a transcriptome signature in PB cells characterized by down-regulation of oxidative phosphorylation genes accompanied by increased serum lactate. Similar gene expression changes were observed in rats and several patients after consuming hepatotoxic doses of APAP. The timing of the changes and the correlation with NAPQI production are consistent with mechanisms known to underlie APAP hepatoxicity. These studies support the further exploration of the blood transcriptome for biomarkers of DILI.

Fannin, R. D., M. Russo, T. M. O'Connell, K. Gerrish, J. H. Winnike, J. Macdonald, J. Newton, S. Malik, S. O. Sieber, J. Parker, R. Shah, T. Zhou, P. B. Watkins and R. S. Paules. Acetaminophen dosing of humans results in blood transcriptome and metabolome changes consistent with impaired oxidative phosphorylation. *Hepatology* 51: 227-236, 2010.

Early-Life Exposures Are Linked to Development of Uterine Fibroids

Summary: Epidemiologists at NIEHS have, for the first time, linked soy formula during infancy, maternal prepregnancy diabetes, low childhood socioeconomic status, and early gestational age at birth to greater risk of early diagnosis of uterine leiomyomata (fibroids) in women.

Abstract: Background: Early-life exposures to hormonally active compounds and other factors may affect later response to estrogen or progesterone and hence may influence development of uterine leiomyomata (fibroids).Objectives: We evaluated associations of in utero and early-life exposures, including soy formula, with self-report of physician-diagnosed fibroids by 35 years of age. Methods: Our study included 19,972 non-Hispanic white women who were 35-59 years of age when they enrolled in the Sister Study in 2003-2007. We estimated risk ratios (RRs) and 95% confidence intervals (CIs) using log-binomial regression models for fibroid associations with adjustment for participant's age and education, maternal age at participant's birth, birth order, and childhood family income.Results: Greater risk of early fibroid diagnosis was associated with soy formula during infancy (RR = 1.25; 95% CI, 0.97-1.61), maternal prepregnancy diabetes (RR = 2.05; 95% CI, 1.16-3.63), low childhood socioeconomic status (RR = 1.28; 95% CI, 1.01-1.63), and gestational age at birth (RR = 1.64; 95% CI, 1.27-2.13, for being born at least 1 month early). In utero diethylstilbestrol (DES) exposure was also associated with early fibroid diagnosis (RR = 1.42; 95% CI, 1.13-1.80), but this association was driven by women reporting probable rather than definite exposure. Conclusions: There are plausible biological pathways by which these early-life factors could promote fibroid pathogenesis. This is the first epidemiologic study to evaluate such exposures, with the exception of in utero DES, in relation to fibroid risk, and replication of findings in other populations is needed. Editor's Summary Uterine leiomyomata (fibroids) are the most common indication for hysterectomies in the United States, but underlying causes of these hormonally responsive benign smooth muscle tumors have not been identified. D'Aloisio et al. (p. 375) hypothesized that early-life exposures that affect uterine development and hormone responses later in life might contribute to fibroid pathogenesis. The authors estimated associations between early fibroid diagnoses (diagnosed by health professional before 36 years of age) among 19,972 non-Hispanic white participants in the Sister Study who were 35-59 years old at enrollment. Early fibroid diagnoses were reported by 8% of study participants, consistent with previous estimates. Adjusted risk ratio estimates (from log-binomial regression models) indicated increased relative risks in association with being fed soy formula during infancy, maternal prepregnancy diabetes, low childhood socioeconomic status, and early birth (at least 1 month before the due date). In utero diethylstilbestrol (DES) exposure was also associated with early fibroid diagnosis, but only among women reporting probable (versus definite) DES exposure. The authors conclude that effects of early life exposures on uterine fibroid pathogenesis are biologically plausible, but note that findings need to be replicated in other study populations.

D'Aloisio, A. A., D. D. Baird, L. A. Deroo and D. P. Sandler. Association of intrauterine and early-life exposures with diagnosis of uterine leiomyomata by 35 years of age in the sister study. *Environ. Health Perspect.,* 118: 375-381, 2010.

Stem Cell Survival Advantage Toward Arsenic Drives Malignant Transformation

Summary: Investigators at NIEHS have found that the carcinogen arsenic targets stem cells for transformation, eventually producing cancers enriched in cancer stem cells (CSCs). This

is facilitated by a stem cell survival advantage toward arsenic during malignant transformation.

Abstract: Background: Arsenic is a carcinogen that targets the urogenital system, including the prostate. Although the mechanisms for arsenic-induced carcinogenesis are undefined, arsenic drives overaccumulation of stem cells and cancer stem cells (CSCs) in vivo and in vitro, indicating that these cells are a key target population. Disruption of stem cell population dynamics may be critical to acquisition of cancer phenotype. We tested the hypothesis that prostate stem cells have a survival selection advantage during arsenic exposure that favors their accumulation and facilitates their malignant transformation. Methods: Innate and acquired resistance to acute (24-72 hours of exposure) and chronic (6 weeks of exposure) arsenite-induced cytolethality and apoptosis were assessed in a human prostate stem cell line (WPE-stem) and the mature parental cell line (RWPE-1). Real-time reverse transcription-polymerase chain reaction and/or Western blot analysis was used to measure the expression of apoptosis-, stress-, and arsenic-related genes. Arsenic-, cadmium-, and N-methyl-N-nitrosourea-induced isogenic malignant transformants of RWPE-1 cells were compared for acquisition of CSC-like qualities by holoclone and sphere formation assays, growth in soft agar, and expression of CSC biomarkers. All statistical tests were two-sided. Results: WPE-stem cells showed innate resistance to arsenic-induced cytolethality (arsenite concentration lethal to 50% of the cells [LC(50)] = 32.4 microM, 95% confidence interval [CI] = 31.5 to 33.3 muM) and apoptosis compared with parental RWPE-1 cells (LC(50) = 10.4 muM, 95% CI = 7.4 to 13.4 microM). Compared with RWPE-1 cells, WPE-stem cells showed noticeably higher expression of antiapoptotic (ie, BCL2, MT), stress-related (ie, NFE2L2, SOD1, PRODH), and arsenic adaptation (ie, ABCC1, GSTP1) factors and noticeably lower expression of proapoptotic factors (ie, BAX, caspases 3, 7, 8, and 9). WPE-stem cells also showed hyper-adaptability to chronic arsenite exposure (5 microM, 6 weeks) compared with RWPE-1 cells (LC(50) = 94.7 vs 32.1 microM, difference = 62.6 muM, 95% CI = 53.3 to 71.9 muM) at levels that in previous work induced a malignant phenotype in RWPE-1 after 30 weeks of exposure. Quantification of CSC-like cells in isogenic RWPE-1 transformants showed that marked overproduction was unique to a malignant phenotype acquired in response to arsenic exposure but not in response to cadmium or N-methyl-N-nitrosourea exposure. Conclusions: An apparent stem cell survival advantage with regard to arsenic causes selection during malignant transformation that manifests itself as an overabundance of CSC-like cells specifically after arsenic-driven acquisition of malignant phenotype. The increased resistance to apoptosis and arsenite hyper-adaptability of WPE-stem cells suggests that arsenite transformation of RWPE-1 cells involves an increase in the number of CSC-like cells.

Tokar, E.J., W. Qu, J. Liu, W. Liu, M. M. Webber, J. M. Phang, and M. P. Waalkes. Arsenic-Specific Stem Cell Selection During Malignant Transformation. *J. Natl. Cancer Inst.,* 102: 638-649, 2010.

Cholesterol Trafficking Linked to Inflammatory Response

Summary: Investigators from NIEHS report that Myeloid Differentiation Primary Response Protein 88 (MyD88), an adaptor protein in innate immunity signaling pathways, is required

for cholesterol export from cells and couples cholesterol export to inflammation. They found that MyD88-dependent inflammatory signals are elicited in macrophages by apolipoprotein A-I (ApoA-I), the major protein component of high-density lipoprotein (HDL) particles.
Abstract: Crosstalk exists in mammalian cells between cholesterol trafficking and innate immune signaling. Apolipoprotein A-I (apoA-I), a serum apolipoprotein that induces antiatherogenic efflux of macrophage cholesterol, is widely described as anti-inflammatory because it neutralizes bacterial lipopolysaccharide. Conversely, lipopolysaccharide-induced inflammation is proatherogenic. However, whether innate immunity plays an endogenous, physiological role in host cholesterol homeostasis in the absence of infection is undetermined. We report that apoA-I signals in the macrophage through Toll-like receptor (TLR)2, TLR4, and CD14, utilizing myeloid differentiation primary response protein 88 (MyD88)-dependent and -independent pathways, to activate nuclear factor-kappaB and induce cytokines. MyD88 plays a critical role in reverse cholesterol transport in vitro and in vivo, in part through promoting ATP-binding cassette A1 transporter upregulation. Taken together, this work identifies apoA-I as an endogenous stimulus of innate immunity that couples cholesterol trafficking to inflammation through MyD88 and identifies innate immunity as a physiologic signal in cholesterol homeostasis.

Smoak, K. A., J. J. Aloor, J. Madenspacher, B. A. Merrick, J. B. Collins, X. Zhu, G. Cavigiolio, M. N. Oda, J. S. Parks and M. B. Fessler. Myeloid Differentiation Primary Response Protein 88 Couples Reverse Cholesterol Transport to Inflammation. *Cell Metab.,* 11: 493-502, 2010.

Oxidized (bi)sulfite leads to reactive sulfur species and protein radical formation

Summary: NIEHS researchers provide evidence that sulfite and (bi)sulfite, commonly used as food preservatives, can be oxidized into reactive free radicals that result in protein oxidative damage. Oxidative damage is proposed to lead to tissue injury in allergic reactions due to byproducts of sulfur dioxide.
Abstract: Background: Sulfur dioxide, formed during the combustion of fossil fuels, is a major air pollutant near large cities. Its two ionized forms in aqueous solution, sulfite and (bi)sulfite, are widely used as preservatives and antioxidants to prevent food and beverage spoilage. (Bi)sulfite can be oxidized by peroxidases to form the very reactive sulfur trioxide anion radical (*SO(3)-). This free radical further reacts with oxygen to form the peroxymonosulfate anion radical (-O(3)SOO*) and sulfate anion radical (SO(4)*-). Objective: To explore the critical role of these radical intermediates in further oxidizing biomolecules, we examined the ability of copper,zinc-superoxide dismutase (Cu,Zn-SOD) to initiate this radical chain reaction, using human serum albumin (HSA) as a model target. Methods: We used electron paramagnetic resonance, optical spectroscopy, oxygen uptake, and immuno-spin trapping to study the protein oxidations driven by sulfite-derived radicals. Results: We found that when Cu,Zn-SOD reacted with (bi)sulfite, *SO(3)- was produced, with the concomitant reduction of SOD-Cu(II) to SOD-Cu(I). Further, we demonstrated that sulfite oxidation mediated by Cu,Zn-SOD induced the formation of radical-derived 5,5-dimethyl-1-pyrroline N-oxide (DMPO) spin-trapped HSA radicals. Conclusions: The present study suggests that protein oxidative damage resulting from (bi)sulfite oxidation

promoted by Cu,Zn-SOD could be involved in oxidative damage and tissue injury in (bi)sulfite-exacerbated allergic reactions.

Ranguelova, K., Bonini, M.G., and Mason, R.P. (Bi)sulfite oxidation by copper, zinc-superoxide dismutase: Sulfite-derived, radical-initiated protein radical formation. *Environ. Health Perspect.,* 118:970-975, 2010.

Genome instability due to ribonucleotide incorporation into DNA

Summary: Researchers at the NIEHS and Umeå University in Sweden established that ribonucleotides are incorporated during replication *in vivo,* the ribonucleotides are normally removed by RNase H2-dependent repair, and defective repair causes cellular stress and genome instability.
Abstract: Maintaining the chemical identity of DNA depends on ribonucleotide exclusion by DNA polymerases. However, ribonucleotide exclusion during DNA synthesis in vitro is imperfect. To determine whether ribonucleotides are incorporated during DNA replication in vivo, we substituted leucine or glycine for an active-site methionine in yeast DNA polymerase ϵ (Pol ϵ). Ribonucleotide incorporation in vitro was three-fold lower for M644L and 11-fold higher for M644G Pol ϵ compared to wild-type Pol ϵ. This hierarchy was recapitulated in vivo in yeast strains lacking RNase H2. Moreover, the pol2-M644G rnh201Δ strain progressed more slowly through S phase, had elevated dNTP pools and generated 2-5-base-pair deletions in repetitive sequences at a high rate and in a gene orientation-dependent manner. The data indicate that ribonucleotides are incorporated during replication in vivo, that they are removed by RNase H2-dependent repair and that defective repair results in replicative stress and genome instability via DNA strand misalignment.

McElhinny, S.A., D. Kumar, A.B. Clark, D.L. Watt, B.E. Watts, E.B. Lundstrom, E. Johansson, A. Chabes and T.A. Kunkel. Genome instability due to ribonucleotide incorporation into DNA. *Nat. Chem. Biol.,* 6: 774-781, 2010.

Gender differences in glucocorticoid-mediated inflammation

Summary: Research performed by scientists from NIEHS and Wake Forest University School of Medicine suggests that glucocorticoids, stress-induced steroids that regulate intermediary metabolism, may contribute to the development, progression, or susceptibility to inflammatory diseases in a gender-specific manner. This finding offers a possible explanation for why more females tend to have certain inflammatory diseases.
Abstract: Males and females show differences in the prevalence of many major diseases that have important inflammatory components to their etiology. These gender-specific diseases, which include autoimmune diseases, hepatocellular carcinoma, diabetes, and osteoporosis, are largely considered to reflect the actions of sex hormones on the susceptibility to inflammatory stimuli. However, inflammation reflects a balance between pro- and anti-inflammatory signals, and investigation of gender-specific responses to the

latter has been neglected. Glucocorticoids are the primary physiological anti-inflammatory hormones in mammals, and synthetic derivatives of these hormones are prescribed as anti-inflammatory agents, irrespective of patient gender. We explored the possibility that sexually dimorphic actions of glucocorticoid regulation of gene expression may contribute to the dimorphic basis of inflammatory disease by evaluating the rat liver, a classic glucocorticoid-responsive organ. Surprisingly, glucocorticoid administration expanded the set of hepatic sexually dimorphic genes. Eight distinct patterns of glucocorticoid-regulated gene expression were identified, which included sex-specific genes. Our experiments also defined specific genes with altered expression in response to glucocorticoid treatment in both sexes, but in opposite directions. Pathway analysis identified sex-specific glucocorticoid-regulated gene expression in several canonical pathways involved in susceptibility to and progression of diseases with gender differences in prevalence. Moreover, a comparison of the number of genes involved in inflammatory disorders between sexes revealed 84 additional glucocorticoid-responsive genes in the male, suggesting that the anti-inflammatory actions of glucocorticoids are more effective in males. These gender-specific actions of glucocorticoids in liver were substantiated in vivo with a sepsis model of systemic inflammation.

Duma, D., J.B. Collins, J.W. Chou and J.A. Cidlowski. Sexually dimorphic actions of glucocorticoids provide a link to inflammatory diseases with gender differences in prevalence. *Sci. Signal.,* 3: ra74, 2010.

Paused Pol II regulates gene activity

Summary: NIEHS investigators demonstrate that transcribed genes globally exhibit pausing of RNA polymerase II (Pol II) during early elongation. The most paused genes have promoter DNA sequences that favor nucleosome assembly and that paused Pol II prevents nucleosome formation to maintain or potentiate gene activity. The investigators also show that promoter-proximal nucleosomes are not required to establish paused Pol II.
Abstract: Metazoan transcription is controlled through either coordinated recruitment of transcription machinery to the gene promoter or regulated pausing of RNA polymerase II (Pol II) in early elongation. We report that a striking difference between genes that use these distinct regulatory strategies lies in the "default" chromatin architecture specified by their DNA sequences. Pol II pausing is prominent at highly regulated genes whose sequences inherently disfavor nucleosome formation within the gene but favor occlusion of the promoter by nucleosomes. In contrast, housekeeping genes that lack pronounced Pol II pausing show higher nucleosome occupancy downstream, but their promoters are deprived of nucleosomes regardless of polymerase binding. Our results indicate that a key role of paused Pol II is to compete with nucleosomes for occupancy of highly regulated promoters, thereby preventing the formation of repressive chromatin architecture to facilitate further or future gene activation.

Gilchrist, D.A., G. Dos Santos, D.C. Fargo, B. Xie, Y. Gao, L. Li, and K. Adelman. Pausing of RNA Polymerase II Disrupts DNA-Specified Nucleosome Organization to Enable Precise Gene Regulation. *Cell* 143: 540-551, 2010.

AWARDS AND HONORS

Scientific Awards

Dr. Karen Adelman (Laboratory of Molecular Carcinogenesis) received the 2010 NIH Directors Award for her seminal work on the mechanism of RNA polymerase stalling.

Dr. Donna Baird (Epidemiology Branch) was elected to the American Epidemiological Society.

Dr. William Copeland (Acting Chief, Laboratory of Molecular Genetics) was selected as Program chair of the Annual International Meeting of the United Mitochondrial Disease Foundation and the Annual Meeting of the Mitochondrial Medicine Society.

Dr. Suzanne Fenton (Cellular and Molecular Pathology Branch) received the Scientific Advisor Award from the International Life Sciences Institute-Health and Environmental Sciences Institute, May 2010.

Dr. Dori Germolec (National Toxicology Program) was awarded Best Paper of the Year 2010 by the Immunotoxicology Specialty Section of the Society of Toxicology for a paper entitled "Influence of cytokine gene variations on immunization to childhood vaccines" in *Vaccine* 27: 6991-6997, 2009.

Dr. Jane Hoppin (Epidemiology Branch) received the US Environmental Protection Agency Bronze Medal for outstanding exposure research support to the interagency Agricultural Health Study.

Dr. David Malarkey (Cellular and Molecular Pathology Branch) was selected as a Notable Alumnus of Tufts University.

Dr. Joan Packenham (Office of Clinical Research) received the 2010 Women of Color STEM Award for Career Achievement in Government.

Dr. Richard Paules (Acting Chief, Laboratory of Toxicology and Pharmacology) received the 2010 Leading Edge in Basic Science Award from the Society of Toxicology.

Dr. Michael Resnick (Laboratory of Molecular Genetics) received the "Phenomenon of Life" Award from the Russian Academy of Medical Sciences.

Dr. Walter Rogan (Epidemiology Branch) is president-elect of the American Epidemiology Society.

Dr. Dale Sandler (Chief, Epidemiology Branch) received the US Environmental Protection Agency Bronze Medal for outstanding exposure research support to the interagency Agricultural Health Study.

Dr. Michel Waalkes (National Toxicology Program) was elected councilor of the Society of Toxicology.

Dr. Sam Wilson (Laboratory of Structural Biology) received the 2010 Environmental Mutagen Society Award.

Named Professorships/Lectures

Dr. Lutz Birnbaumer (Laboratory of Neurobiology) was the keynote speaker at Berlin Brain Days 2010, the 7th International Neuroscience PhD Symposium, Berlin, Germany.

Dr. John Cidlowski (Chief, Laboratory of Signal Transduction) was the keynote speaker at the 2nd Serbian Congress of Endocrinology.

Dr. Perry Blackshear (Laboratory of Signal Transduction) presented the Astor Lectureship at the University of Oxford, and the plenary address at the Chilean Society of Neuroscience, Valdivia, Chile.

Dr. Jan Drake (Laboratory of Molecular Genetics) delivered the Keynote Address to the XIV Latin American Congress of Genetics in Viña del Mar, Chile.

Dr. Steven Kleeberger (Acting Deputy Director; Laboratory of Respiratory Biology) presented the 2010 William B. Kinter Memorial Lecture at the Mount Desert Island Biological Laboratory.

Dr. Thomas Kunkel (Chief, Laboratory of Structural Biology; Laboratory of Molecular Genetics) was keynote speaker at the International Conference on Radiation and Cancer Biology, Nagasaki, and at the 4th Baltimore Area Repair Symposium, Baltimore, MD. He presented the Harris Lecture, Massachusetts Institute of Technology, Cambridge, MA.

Dr. Stephanie London (Epidemiology Branch; Laboratory of Respiratory Biology) presented a Plenary Lecture at the Annual Meeting of the American Academy of Allergy, Asthma and Immunology in February 2010.

Dr. Ronald Mason (Laboratory of Toxicology and Pharmacology) present the Brucher Lecture at the 25th Meeting of the Electron Spin Resonance Spectroscopy Group of the Royal Society of Chemistry.

Dr. David Miller (Acting Scientific Director) was the keynote speaker at the Barriers of the Central Nervous System Gordon Conference.

Dr. Jim Putney (Laboratory of Signal Transduction) was a Visiting Professor, Department of Physiology, University of Paris-sud, Orsay, France.

Dr. Dale Sandler (Chief, Epidemiology Branch) presented the Keynote Address at the 2010 National Latino Cancer Summit.

Dr. William Stokes (National Toxicology Program) presented the keynote address at the International Symposium of the Korean Center for the Validation of Alternative Methods and at the 22nd Annual Meeting of the Japanese Society for Alternatives to Animal Experiments.

Dr. Ken Tomer (Laboratory of Structural Biology) presented the keynote address at the 1st International Meeting of the Romanian Society for Mass Spectrometry in Sinaia, Romania.

Dr. Clarice Weinberg (Chief, Biostatistics Branch) presented the Lowell Reed Lecture at the annual meeting of the American Public Health Association.

Dr. Allen Wilcox (Epidemiology Branch) will present the plenary lecture at the Third North American Congress of Epidemiology.

Dr. Sam Wilson (Laboratory of Structural Biology) was the plenary speaker at the L.S. Skaggs Biomedical Research Symposium, University of California-San Diego, San Diego, and presented the keynote address at the International Conference on Biomedical and Environmental Science and Technology, Beijing.

Dr. Darryl Zeldin (Acting Clinical Director; Laboratory of Respiratory Biology) was a Keynote speaker at the 110th Anniversary Celebration of Tongji Medical College, Huazhong University of Science and Technology, and will give the Plenary Lecture at the 12th International Conference on Bioactive Lipids in Cancer, Inflammation and Related Diseases.

Scientific Advisory Boards

Dr. William Copeland (Acting Chief, Laboratory of Molecular Genetics) served chair of the Research and Policy Review Committee, United Mitochondrial Disease Foundation.

Dr. Darlene Dixon (Cellular and Molecular Pathology Branch) served as a Scientific Advisor to the Emerging Issues Steering Committee of the International Life Sciences Institute-Health and Environmental Sciences Institute.

Dr. Suzanne Fenton (Cellular and Molecular Pathology Branch) served on the Inter-Agency Breast Cancer and the Environment Research Coordinating Committee; the US EPA Scientific Advisory Panel for Atrazine; served as Grant Review Chair, California Breast Cancer Research Program, Special Research Initiatives, Epidemiological cohorts and early life exposures; and as international lead on OECD and US EPA Extended One-Gen Reproductive Toxicology test guidelines.

Dr. Stephanie London (Epidemiology Branch and Laboratory of Respiratory Biology) served on the Health Effects Institute Review Committee.

Dr. Matthew Longley (Laboratory of Molecular Genetics) served as a grant reviewer for the European Research Council Life Science Panel.

Dr. Robert Sills (Chief, Cellular and Molecular Pathology Branch) organized and co-chaired the Society of Toxicologic Pathology and the International Federation of Societies of Toxicologic Pathologists meeting on Neuropathology.

Dr. Sam Wilson (Laboratory of Structural Biology) served on the scientific advisory boards of Burroughs Wellcome Fund Training Program, The University of Texas Health Science Center at Houston; The Netherlands Toxicogenomics Center; and FAMRI Center, Weizmann Institute of Science, Rehovot, Israel; and served as co-Chair, 4th Biannual Japan-US/US-Japan DNA Repair Meeting.

Editorial Boards

Dr. Karen Adelman (Laboratory of Molecular Carcinogenesis) served on the editorial board of *Transcription.*

Dr. Suzanne Fenton (Cellular and Molecular Pathology Branch) served as associate editor of *Reproductive Toxicology.*

Dr. Michael Fessler (Laboratory of Respiratory Biology) served on the editorial board of *PLoS One.*

Dr. Paul Foster (National Toxicology Program) served on the editorial board of *Birth Defects Research*.

Dr. Joyce Goldstein (Laboratory of Toxicology and Pharmacology) served on the editorial boards of *Drug Metabolism and Disposition* and *Drug Metabolism Reviews.*

Dr. Dmitri Gordenin (Laboratory of Molecular Genetics) served on the editorial board of *Mutation Research*.

Dr. Leping Li (Biostatistics Branch) served on the editorial boards of the *Journal of the Indian Society of Agricultural Statistics* and the *Journal of Biometrics and Biostatistics.*

Dr. Stephanie London (Epidemiology Branch and Laboratory of Respiratory Biology) served as editor of the journal *Epidemiology.*

Dr. David Miller (Acting Scientific Director) served as associate editor of the *Journal of Experimental Zoology* and the *Journal of Experimental Pharmacology and Therapeutics*. He also served on the editorial boards of the *American Journal of Physiology: Regulatory, Integrative and Comparative Physiology*, *Toxicology and Applied Pharmacology*, *Cerebrospinal Fluid Research*, and *Frontiers in Pharmacology*.

Dr. Richard Paules (Acting Chief, Laboratory of Toxicology and Pharmacology) served as associate editor of *Physiological Genomics* and on the editorial board of *Environmental Health Perspectives.*

Dr. Lee Pedersen (Laboratory of Structural Biology) served on the editorial boards of the *World Journal of Biological Chemistry* and *Biophysical Chemistry.*

Dr. Jim Putney (Laboratory of Signal Transduction) served on the editorial boards of the *American Journal of Physiology* and *Cell Calcium.*

Dr. Lisa Rider (Office of Clinical Research) served on the editorial boards of *The Open Rheumatology Journal* and the *International Journal of Rheumatology.*

Dr. Roel Schaaper (Laboratory of Molecular Genetics) served on the editorial board of *Mutation Research.*

Dr. Robert Sills (Chief, Cellular and Molecular Pathology Branch) serves as associate editor for Environmental Pathobiology, *Veterinary Pathology*.

Dr. Michel Waalkes (National Toxicology Program) served as associate editor of *Environmental Health Perspectives* and on the editorial advisory board of *Chemical Research in Toxicology.*

Dr. Nigel Walker (National Toxicology Program) served on the editorial board of *Toxicology and Applied Pharmacology.*

Dr. Sam Wilson (Laboratory of Structural Biology) served as associate editor of *DNA Repair*; and on the editorial boards of *Nucleic Acids Research* and *Mechanisms of Ageing and Development.*

Dr. Jerrel Yakel (Laboratory of Neurobiology) served as senior editor of the *Journal of Physiology.*

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, American Journal of Respiratory Cell and Molecular Biology, Prostaglandins and Other Lipid Mediators, The Open Environmental Journal,* and *Molecular and Cellular Pharmacology.*