Division of Intramural Research

NAEHS Council Update

February 2014

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. A Candidate has not yet been identified.

Investigators in the areas of Molecular and Cellular Signaling, Neuroscience, and Developmental or Reproductive Biology
The National Institute of Environmental Health Sciences is recruiting for multiple full-time appointments at either the tenure-track or tenure-eligible level in the areas of Molecular and Cellular Signaling, Neuroscience, and Developmental or Reproductive Biology. The successful candidates are expected to lead innovative, independent research programs on any fundamental aspect of research in the above three areas of interest which form a basis for understanding the effects of the environment on human health. Applicants should have a Ph.D., M.D. or equivalent doctoral degree with at least 3 years of postdoctoral research experience in their field and an outstanding publication record. The emphasis will be on identifying exceptional scientists with innovative and productive research programs. Evaluation of applications will begin on February 3, 2014. Dr. Trevor Archer, Chief, Laboratory of Molecular Carcinogenesis, is chair of the search committee.

Investigators in the areas of Biostatistics, Bioinformatics, and Computational Biology
The National Institute of Environmental Health Sciences is recruiting for multiple full-time appointments at either the tenure-track or tenure-eligible level in the areas of biostatistics,

bioinformatics, and computational biology. The successful candidate will develop and direct a high-quality, independent research program on analytic methods applicable to understanding the effects of the environment on human health. Applicants should have a Ph.D. or equivalent doctoral degree and a proven record in the development of analytic methods with biomedical application. Experience working with epidemiologic or high dimensional genetic, epigenetic, and genomic datasets is highly desirable, but not required. Evaluation of applications will begin on or about February 10, 2014. Dr. Jack A. Taylor, Epidemiology Branch and Laboratory of Molecular Carcinogenesis, is chair of the search committee.

NEWLY TENURED DIR PRINCIPAL INVESTIGATORS

At the November 18, 2013 meeting of the NIH Central Tenure Committee held in Bethesda **Dr. Honglei Chen** from the Epidemiology Branch and **Dr. Michael Fessler** from the Laboratory of Respiratory Biology were awarded tenure.

DIR RESEARCH UPDATE

Research on Parkinson's Pre-Motor Symptoms

Honglei Chen, M.D., Ph.D.

Epidemiology Branch, DIR, NIEHS

The aim of my research is to identify environmental factors that contribute to neurodegenerative diseases and aging, and to understand the natural history of debilitating neurodegenerative diseases. The ultimate goal is disease prevention and healthy aging. In pursuit of these goals, I have chosen to focus on Parkinson's disease (PD) – the second most prevalent neurodegenerative condition after Alzheimer's. My research has contributed to the documentation of a wide range of environmental (e.g. smoking, caffeine intake, exercise, pesticides, certain medications) and genetic (e.g. ~30 loci from recent GWAS analyses) risk factors for PD. PD may take decades to develop and to date all efforts to cure PD have failed. It is already too late to intervene at the time of PD motor/clinical onset; therefore, it is of ultimate importance to investigate the origins of the disease and to understand its early etiological process. I therefore recently shifted my research focus to a group of non-specific symptoms that may precede PD motor onset by years. These "pre-motor" symptoms include hyposmia, depression/anxiety, rapid eye movement sleep behavior disorder, excessive daytime sleepiness, and constipation. Accumulating evidence from clinical, epidemiological, and experimental research suggests that these symptoms may occur in the prodromal stage of PD. The Braak hypothesis further provides pathological underpins that these symptoms may be related to Lewy pathology in the brain and even in the periphery before the involvement of substantia nigra pars compacta. Therefore, research on pre-motor symptoms of PD may offer an excellent opportunity to characterize high-risk populations for PD and to better understand the origin and etiology of the disease. More importantly, such research may lead to evaluation of novel etiological hypotheses such as the possibility that environmental toxicants or viruses may initiate PD pathogenesis in the gastrointestinal tract or olfactory bulb. In this presentation, I will discuss my ongoing and future research on PD pre-motor symptoms and discuss potential gains and obstacles of research on PD pre-motor symptoms.

DIR RESEARCH UPDATE

Regulation of the Innate Immune Response to Environment by Cholesterol Trafficking

Michael B. Fessler, M.D.

Laboratory of Respiratory Biology, DIR, NIEHS

The Clinical Investigation of Host Defense Group investigates molecular and cellular mechanisms of the innate immune response to environmental 'pathogen-associated molecular patterns' (e.g., lipopolysaccharide [LPS]), using the macrophage and the lung as in vitro and in vivo model systems, with the ultimate aim of translating our findings to human disease. Within this platform, our focus is in defining novel areas of crosstalk between the innate immune response and cholesterol trafficking. Our central hypothesis is that cholesterol trafficking and innate immunity signaling are intrinsically coupled processes, and that perturbations in each therefore regulate the other. Our laboratory's major directive is that the manipulation/perturbation of cell cholesterol will yield novel: 1) mechanisms underlying the induction and regulation of the innate immune response; 2) determinants of inflammatory phenotype in human subjects; and 3) sites for intervening in innate immunity and the diseases in which it plays a role. To this end, we have shown in cellular and in vivo rodent model systems that innate immune signals are required for homeostatic cholesterol transport, and, conversely, that homeostatic regulation of cholesterol levels in 'lipid raft' microdomains of the plasma membrane of leukocytes critically regulates innate immune signal transduction. Applying proteomic analyses to lipid raft preparations from macrophages, we have also defined novel cholesterol-sensitive signaling responses of the cell to LPS, and novel molecular targets that regulate LPS signal transduction. Pursuing the hypothesis that cholesterol trafficking through the lung – an organ not traditionally conceived of as cholesterol-sensitive – regulates immune responses to the environment, we have reported that several genetic and chemical manipulations of lung cholesterol trafficking in fact robustly impact pulmonary innate and adaptive immune responses. Last, we have used primary human leukocytes and epidemiologic tools to confirm several of our hypotheses in human health and disease. Given the high prevalences of dyslipidemia and inflammatory lung disease in modern society and the translational nature of our program, our studies have strong potential for ultimately impacting both public health and the clinical care of individual patients.

GRANTS RECEIVED BY DIR PRINCIPAL INVESTIGATORS

Title: Epigenetic Biomarkers of Tobacco Smoke Exposure.
PI: Douglas A. Bell, Ph.D., Laboratory of Molecular Genetics
Granting Agency: Food and Drug Administration Center for Tobacco Products via the NIH Intramural Center for Tobacco Regulatory Science
Grant Period: 2013-2015
Total Award: $1,500,000

Title: Maternal smoking in pregnancy, methylation, and asthma in offspring
PI: Stephanie J. London, M.D., Dr.P.H., Epidemiology Branch and Laboratory of Respiratory Biology
Granting Agency: Food and Drug Administration Center for Tobacco Products via the NIH Intramural Center for Tobacco Regulatory Science
Grant Period: 2013-2015
Total Award: $1,307,934

Title: Role of IGF1R in hippocampal CA2 plasticity and function: interaction with MeCP2
PI: Serena Dudek, Ph.D., Laboratory of Neurobiology
Granting Agency: International Rett Syndrome Foundation
Grant Period: 2014-2015
Total Award: $98,000

NIEHS SCIENCE DAYS

The Eleventh Annual NIEHS Science Days were held on November 7-8, 2013, 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 Genomics and the Environment 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, 100 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: Dale P. Sandler, Ph.D., Epidemiology Branch
Fellow of the Year: Steven A. Roberts, Ph.D., Laboratory of Molecular Genetics
Best Poster Presentation:

1. Matthew J. Young, Ph.D., Laboratory of Molecular Genetics, "The Complexity of Heterozygous POLG2 Mutations Associated with Human Mitochondrial Disease."
2. Steven A. Roberts, Ph.D., Laboratory of Molecular Genetics, "Hyper-mutation of single stranded DNA across yeast and cancer genomes."
3. Benjamin S. Scruggs, Ph.D., Laboratory of Molecular Carcinogenesis, "Pausing of RNA Polymerase II at Enhancers."
4. Salik Hussain, Ph.D., Office of Clinical Research, "Human bronchial epithelia exposure to multi-walled carbon nanotubes induces inflammasome-dependent pyroptosis and a profibrotic response."
5. Brad Lackford, Laboratory of Molecular Carcinogenesis, "Fip1 regulates mRNA alternative polyadenylation to promote stem cell self-renewal."
6. Shannon L. Farris, Ph.D., Laboratory of Neurobiology, "Spatial exploration induces immediate early gene expression in rat hippocampal area CA2."
7. Monica Frazier, Laboratory of Molecular Genetics, "Mutational Consequences of dgt Overexpression."
8. Sylvia C. Hewitt, Laboratory of Reproductive & Developmental Toxicology, "Mouse Models to Evaluate Estrogen Receptor-α DNA Binding Dependent Signaling Mechanisms: ERE Binding Deficient vs. DNA Binding Deficient."
9. Yuanyuan Li, Ph.D., Biostatistics Branch, "T-KDE: A method for genome-wide identification of constitutive protein binding sites from multiple ChIP-seq data sets."

Best Oral Presentation: Sabrina E. Robertson, Ph.D., Laboratory of Neurobiology, "Developmental origins of central norepinephrine neuron diversity.

DIR PAPERS OF THE YEAR FOR 2013

Williams JS, Smith DJ, Marjavaara L, Lujan SA, Chabes A, Kunkel TA. Topoisomerase 1-mediated removal of ribonucleotides from nascent leading-strand DNA. *Mol. Cell,* 49: 1010-1015, 2013.

> RNase H2-dependent ribonucleotide excision repair (RER) removes ribonucleotides incorporated during DNA replication. When RER is defective, ribonucleotides in the nascent leading strand of the yeast genome are associated with replication stress and genome instability. Here, we provide evidence that topoisomerase 1 (Top1) initiates an independent form of repair to remove ribonucleotides from genomic DNA. This Top1-dependent process activates the S phase checkpoint. Deleting TOP1 reverses this checkpoint activation and also relieves replication stress and genome instability in RER-defective cells. The results reveal an additional removal pathway for a very common lesion in DNA, and they imply that the "dirty" DNA ends created when Top1 incises ribonucleotides in DNA are responsible for the adverse consequences of ribonucleotides in RNase H2-defective cells.

Madenspacher JH, Azzam KM, Gowdy KM, Malcolm KC, Nick JA, Dixon D, Aloor JJ, Draper DW, Guardiola JJ, Shatz M, Menendez D, Lowe J, Lu J, Bushel P, Li L, Merrick BA, Resnick MA, Fessler MB. p53 Integrates host defense and cell fate during bacterial pneumonia. *J. Exp. Med.,* 210: 891-904, 2013.

> Cancer and infection are predominant causes of human mortality and derive, respectively, from inadequate genomic and host defenses against environmental agents. The transcription factor p53 plays a central role in human tumor suppression. Despite its expression in immune cells and broad responsiveness to stressors, it is virtually unknown whether p53 regulates host defense against infection. We report that the lungs of naive p53(-/-) mice display genome-wide induction of NF-κB response element-enriched proinflammatory genes, suggestive of type 1 immune priming. p53-null and p53 inhibitor-treated mice clear Gram-negative and -positive bacteria more effectively than controls after intrapulmonary infection. This is caused, at least in part, by cytokines produced by an expanded population of apoptosis-resistant, TLR-hyperresponsive alveolar macrophages that enhance airway neutrophilia. p53(-/-) neutrophils, in turn, display heightened phagocytosis, Nox-dependent oxidant generation, degranulation, and bacterial killing. p53 inhibition boosts bacterial killing by mouse neutrophils and oxidant generation by human neutrophils. Despite enhanced bacterial clearance, infected p53(-/-) mice suffer increased mortality associated with aggravated lung injury. p53 thus modulates host defense through regulating microbicidal function and fate of phagocytes, revealing a fundamental link between defense of genome and host during environmental insult.

Xu Z, Bolick SC, DeRoo LA, Weinberg CR, Sandler DP, Taylor JA. Epigenome-wide association study of breast cancer using prospectively collected sister study samples. *J. Natl. Cancer Inst.,* 105: 694-700, 2013.

BACKGROUND: Previous studies have suggested DNA methylation in blood is a potential epigenetic marker of cancer risk, but this has not been evaluated on a genome-wide scale in prospective studies for breast cancer.
METHODS: We measured DNA methylation at 27578 CpGs in blood samples from 298 women who developed breast cancer 0 to 5 years after enrollment in the Sister Study cohort and compared them with a random sample of 612 cohort women who remained cancer free. We also genotyped women for nine common polymorphisms associated with breast cancer.
RESULTS: We identified 250 differentially methylated CpGs (dmCpGs) between case subjects and noncase subjects (false discovery rate [FDR] $Q < 0.05$). Of these dmCpGs, 75.2% were undermethylated in case subjects relative to noncase subjects. Women diagnosed within 1 year of blood draw had small but consistently greater divergence from noncase subjects than did women diagnosed at more than 1 year. Gene set enrichment analysis identified Kyoto Encyclopedia of Genes and Genomes cancer pathways at the recommended FDR of Q less than 0.25. Receiver operating characteristic analysis estimated a prediction accuracy of 65.8% (95% confidence interval = 61.0% to 70.5%) for methylation, compared with 56.0% for the Gail model and 58.8% for genome-wide association study polymorphisms. The prediction accuracy of just five dmCpGs (64.1%) was almost as good as the larger panel and was similar (63.1%) when replicated in a small sample of 81 women with diverse ethnic backgrounds.
CONCLUSIONS: Methylation profiling of blood holds promise for breast cancer detection and risk prediction.

Freudenthal BD, Beard WA, Shock DD, Wilson SH. Observing a DNA polymerase choose right from wrong. *Cell*, 154: 157-168, 2013.

DNA polymerase (pol) β is a model polymerase involved in gap-filling DNA synthesis utilizing two metals to facilitate nucleotidyl transfer. Previous structural studies have trapped catalytic intermediates by utilizing substrate analogs (dideoxy-terminated primer or nonhydrolysable incoming nucleotide). To identify additional intermediates during catalysis, we now employ natural substrates (correct and incorrect nucleotides) and follow product formation in real time with 15 different crystal structures. We are able to observe molecular adjustments at the active site that hasten correct nucleotide insertion and deter incorrect insertion not appreciated previously. A third metal binding site is transiently formed during correct, but not incorrect, nucleotide insertion. Additionally, long incubations indicate that pyrophosphate more easily dissociates after incorrect, compared to correct, nucleotide insertion. This appears to be coupled to subdomain repositioning that is required for catalytic activation/deactivation. The structures provide insights into a fundamental chemical reaction that impacts polymerase fidelity and genome stability.

Robertson SD, Plummer NW, de Marchena J, Jensen P. Developmental origins of central norepinephrine neuron diversity. *Nat. Neurosci.,* 16: 1016-1023, 2013.

Central norepinephrine-producing neurons comprise a diverse population of cells differing in anatomical location, connectivity, function and response to disease and environmental insult. The mechanisms that generate this diversity are unknown. Here we elucidate the lineal relationship between molecularly distinct progenitor populations in the developing mouse

hindbrain and mature norepinephrine neuron subtype identity. We have identified four genetically separable subpopulations of mature norepinephrine neurons differing in their anatomical location, axon morphology and efferent projection pattern. One of the subpopulations showed an unexpected projection to the prefrontal cortex, challenging the long-held belief that the locus coeruleus is the sole source of norepinephrine projections to the cortex. These findings reveal the embryonic origins of central norepinephrine neurons and provide multiple molecular points of entry for future study of individual norepinephrine circuits in complex behavioral and physiological processes including arousal, attention, mood, memory, appetite and homeostasis.

Roberts SA, Lawrence MS, Klimczak LJ, Grimm SA, Fargo D, Stojanov P, Kiezun A, Kryukov GV, Carter SL, Saksena G, Harris S, Shah RR, Resnick MA, Getz G, Gordenin DA. An APOBEC cytidine deaminase mutagenesis pattern is widespread in human cancers. *Nat. Genetics,* 45: 970-976, 2013.

Recent studies indicate that a subclass of APOBEC cytidine deaminases, which convert cytosine to uracil during RNA editing and retrovirus or retrotransposon restriction, may induce mutation clusters in human tumors. We show here that throughout cancer genomes APOBEC-mediated mutagenesis is pervasive and correlates with APOBEC mRNA levels. Mutation clusters in whole-genome and exome data sets conformed to the stringent criteria indicative of an APOBEC mutation pattern. Applying these criteria to 954,247 mutations in 2,680 exomes from 14 cancer types, mostly from The Cancer Genome Atlas (TCGA), showed a significant presence of the APOBEC mutation pattern in bladder, cervical, breast, head and neck, and lung cancers, reaching 68% of all mutations in some samples. Within breast cancer, the HER2-enriched subtype was clearly enriched for tumors with the APOBEC mutation pattern, suggesting that this type of mutagenesis is functionally linked with cancer development. The APOBEC mutation pattern also extended to cancer-associated genes, implying that ubiquitous APOBEC-mediated mutagenesis is carcinogenic.

Zeron-Medina J, Wang X, Repapi E, Campbell MR, Su D, Castro-Giner F, Davies B, Peterse EF, Sacilotto N, Walker GJ, Terzian T, Tomlinson IP, Box NF, Meinshausen N, De Val S, Bell DA, Bond GL. A polymorphic p53 response element in KIT ligand influences cancer risk and has undergone natural selection. *Cell*, 155: 410-422, 2013.

The ability of p53 to regulate transcription is crucial for tumor suppression and implies that inherited polymorphisms in functional p53-binding sites could influence cancer. Here, we identify a polymorphic p53 responsive element and demonstrate its influence on cancer risk using genome-wide data sets of cancer susceptibility loci, genetic variation, p53 occupancy, and p53-binding sites. We uncover a single-nucleotide polymorphism (SNP) in a functional p53-binding site and establish its influence on the ability of p53 to bind to and regulate transcription of the KITLG gene. The SNP resides in KITLG and associates with one of the largest risks identified among cancer genome-wide association studies. We establish that the SNP has undergone positive selection throughout evolution, signifying a selective benefit, but go on to show that similar SNPs are rare in the genome due to negative selection, indicating that polymorphisms in p53-binding sites are primarily detrimental to humans.

Mueller GA, Pedersen LC, Lih FB, Glesner J, Moon AF, Chapman MD, Tomer KB, London RE, Pomés A. The novel structure of the cockroach allergen Bla g 1 has implications for allergenicity and exposure assessment. *J. Allergy Clin. Immunol.,* 132: 1420-1426.e9, 2013.

BACKGROUND: Sensitization to cockroach allergens is a major risk factor for asthma. The cockroach allergen Bla g 1 has multiple repeats of approximately 100 amino acids, but the fold of the protein and its biological function are unknown.
OBJECTIVE: We sought to determine the structure of Bla g 1, investigate the implications for allergic disease, and standardize cockroach exposure assays.
METHODS: nBla g 1 and recombinant constructs were compared by using ELISA with specific murine IgG and human IgE. The structure of Bla g 1 was determined by x-ray crystallography. Mass spectrometry and nuclear magnetic resonance spectroscopy were used to examine the ligand-binding properties of the allergen.
RESULTS: The structure of an rBla g 1 construct with comparable IgE and IgG reactivity to the natural allergen was solved by x-ray crystallography. The Bla g 1 repeat forms a novel fold with 6 helices. Two repeats encapsulate a large and nearly spherical hydrophobic cavity, defining the basic structural unit. Lipids in the cavity varied depending on the allergen origin. Palmitic, oleic, and stearic acids were associated with nBla g 1 from cockroach frass. One unit of Bla g 1 was equivalent to 104 ng of allergen.
CONCLUSIONS: Bla g 1 has a novel fold with a capacity to bind various lipids, which suggests a digestive function associated with nonspecific transport of lipid molecules in cockroaches. Defining the basic structural unit of Bla g 1 facilitates the standardization of assays in absolute units for the assessment of environmental allergen exposure.

Lai AY, Mav D, Shah R, Grimm SA, Phadke D, Hatzi K, Melnick A, Geigerman C, Sobol SE, Jaye DL, Wade PA. DNA methylation profiling in human B cells reveals immune regulatory elements and epigenetic plasticity at Alu elements during B-cell activation. *Genome Res.,* 23: 2030-2041, 2013.

Memory is a hallmark of adaptive immunity, wherein lymphocytes mount a superior response to a previously encountered antigen. It has been speculated that epigenetic alterations in memory lymphocytes contribute to their functional distinction from their naive counterparts. However, the nature and extent of epigenetic alterations in memory compartments remain poorly characterized. Here we profile the DNA methylome and the transcriptome of B-lymphocyte subsets representing stages of the humoral immune response before and after antigen exposure in vivo from multiple humans. A significant percentage of activation-induced losses of DNA methylation mapped to transcription factor binding sites. An additional class of demethylated loci mapped to Alu elements across the genome and accompanied repression of DNA methyltransferase 3A. The activation-dependent DNA methylation changes were largely retained in the progeny of activated B cells, generating a similar epigenetic signature in downstream memory B cells and plasma cells with distinct transcriptional programs. These findings provide insights into the methylation dynamics of the genome during cellular differentiation in an immune response.

Bertelsen RJ, Brantsæter AL, Magnus MC, Haugen M, Myhre R, Jacobsson B, Longnecker MP, Meltzer HM, London SJ. Probiotic milk consumption in pregnancy and infancy and subsequent childhood allergic diseases. *J. Allergy Clin. Immunol.,* 133: 165-171.e8., 2014.

BACKGROUND: Whether probiotics, which can influence the microbiome, prevent infant eczema or allergic disease remains an open question. Most studies have focused on high-risk infants.
OBJECTIVES: We sought to assess whether consumption of probiotic milk products protects against atopic eczema, rhinoconjunctivitis, and asthma in early childhood in a large population-based pregnancy cohort (the Norwegian Mother and Child Cohort study).
METHODS: We examined associations between consumption of probiotic milk products in pregnancy and infancy with questionnaire-reported atopic eczema, rhinoconjunctivitis, and asthma in 40,614 children. Relative risks (RRs) were calculated by using general linear models adjusted for potential confounders.
RESULTS: Consumption of probiotic milk in pregnancy was associated with a slightly reduced relative risk (RR) of atopic eczema at 6 months (adjusted RR, 0.94; 95% CI, 0.89-0.99) and of rhinoconjunctivitis between 18 and 36 months (adjusted RR, 0.87; 95% CI, 0.78-0.98) compared with no consumption during pregnancy. Maternal history of allergic disease did not notably influence the associations. When both the mother (during pregnancy) and infant (after 6 months of age) had consumed probiotic milk, the adjusted RR of rhinoconjunctivitis was 0.80 (95% CI, 0.68-0.93) relative to no consumption by either. Probiotic milk consumption was not associated with asthma at 36 months.
CONCLUSIONS: In this population-based cohort consumption of probiotic milk products was related to a reduced incidence of atopic eczema and rhinoconjunctivitis, but no association was seen for incidence of asthma by 36 months of age.

AWARDS AND HONORS

Scientific Awards

Dr. John Cidlowski (Chief, Laboratory of Signal Transduction) received the 2013 Allan Munck Award from Dartmouth Medical School.

Dr. Mitch Eddy (Laboratory of Reproductive and Developmental Toxicology) was awarded the 2013 Distinguished Service Award from the Society for the Study of Reproduction.

Dr. Kathy Laber (Chief, Comparative Medicine Branch) served as Past President of AALAS (American Association for Laboratory Animal Science).

Dr. Fredrick Miller (Office of Clinical Research) was elected to Best Doctors in America and received the 2013 U.S. Public Health Service Achievement Medal.

Dr. Shyamal Peddada (Biostatistics Branch) received the 2013 PV Sukhatme Gold Medal from the Indian Society of Agricultural Statistics for making "significant contributions in Statistics/Agricultural Statistics".

Dr. Douglas Ganini da Silva (Laboratory of Toxicology and Pharmacology) received the Larry Oberley Young Investigator Award from the Society of Free Radical Biology and Medicine.

Named Professorships/Lectures

Dr. William Copeland (Chief, Laboratory of Molecular Genetics) was Chair for Mitochondrial DNA Maintenance, 11th International Conference on Environmental Mutagens 2013 meeting, Foz do Iguacu, PR, Brazil.

Dr. Patricia Jensen (Laboratory of Neurobiology) was invited to present the Plenary Lecture at the Second Annual Neural Circuit Colloquium in Montpellier, France.

Dr. Thomas Kunkel (Laboratory of Structural Biology, Laboratory of Molecular Genetics) presented the Keynote Address at Graduate Research Day, University of Maryland Eastern Shore; and Plenary Lecture at the Conference on “DNA polymerases: biology, diseases and biomedical applications”, Cambridge, UK.

Dr. Stephanie London (Epidemiology Branch) will give the Charles & Edith McGill Lectureship in Occupational and Environmental Medicine at Vanderbilt University School of Medicine, Nashville, Tennessee.

Dr. David Miller (Chief, Laboratory of Toxicology and Pharmacology) was the Keynote Speaker at the Science in the Mountains meeting held at Appalachian State University, Boone, NC.

Dr. Fredrick Miller (Office of Clinical Research) presented the Keynote Address at the 5th International Myositis Workshop, Tokyo, Japan; and the Keynote Address at the 13th International Workshop on Scleroderma Research, Boston, MA.

Dr. Geoffrey Mueller (Laboratory of Structural Biology) was the Plenary Speaker, International Symposium of the Ph.D. Program Immunity in Cancer and Allergy, University of Salzburg, Austria.

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

Advisory/Editorial Boards

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

Dr. Jonathan Freedman (Laboratory of Toxicology and Pharmacology) was appointed to the Editorial Board of *PLOS One*.

Dr. Stavros Garantziotis (Clinical Research Unit, Laboratory of Respiratory Biology) served on the Editorial Boards of the *American Journal of Physiology – Lung Cellular and Molecular Physiology* and *American Journal of Respiratory Cell and Molecular Biology*.

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

Dr. Stephanie London (Epidemiology Branch) serves on the Scientific Advisory Board for the Helmholtz Institute, Munich Germany. She also serves as an Associate Editor of *Environmental Health Perspectives* and an Editor of *Epidemiology*.

Dr. Ronald Mason (Laboratory of Toxicology and Pharmacology) served on the Advisory Board of The National Biomedical EPR Center at the Medical College of Wisconsin; and on the Editorial Boards of *Chemico-Biological Interactions*, *Free Radical Biology and Medicine*, *Spectroscopy* and *Research in Chemical Toxicology*.

Dr. Fredrick Miller (Office of Clinical Research) served as Associate Editor of the *Journal of Neuromuscular Diseases*.

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

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

Dr. Humphrey Yao (Laboratory of Reproductive and Developmental Toxicology) served as an Associate Editor for *Biology of Reproduction* and served on the Editorial Board of *Endocrinology*.

MENTORING

Dr. Douglas Caruana, a visiting fellow in the Laboratory of Neurobiology, has accepted a faculty position in the UK. His mentor was Serena Dudek.

Dr. Georgette Charles a postdoctoral fellow in the Laboratory of Molecular Carcinogenesis accepted a position at AVOS Consulting in Raleigh, N.C., a division of INC Research that specializes in strategic and financial market analysis for life sciences companies. Her mentor was Guang Hu.

Dr. Jennifer Cheng a postdoctoral fellow in the Laboratory of Respiratory Biology accepted a position as a now a Research Associate at Hospital for Special Surgery, New York, NY. Her mentor was Darryl Zeldin.

Dr. Shay Covo a postdoctoral fellow in the Laboratory of Molecular Genetics accepted a position as an Assistant Professor in the Department of Plant Pathology and Microbiology at The Hebrew University of Jerusalem in Israel. His mentor was Michael Resnick.

Dr. Huaixin Dang a postdoctoral fellow in the Laboratory of Respiratory Biology accepted a position as Principle Scientist, In vivo pharmacology, Cardiovascular and Metabolic Diseases, WuXi AppTec Co., Ltd., Shanghai, China. His mentor was Anton Jetton.

Dr. Heather Franco, an IRTA fellow in the Laboratory of Reproductive and Developmental Toxicology accepted a position as a Proposal Developer at Quintiles, in Durham, NC. Her mentor was Humphrey Yao.

Dr. Ashley Godfrey a postdoctoral trainee in the Epidemiology Branch accepted a position at the Duke Cancer Institute as a scientific review officer. In her new role, Godfrey will review oncology clinical research protocols, involving human subjects, for scientific merit and appropriateness. Her mentor was Jack Taylor.

Dr. Nikhil Gokhale a visiting fellow in the Laboratory of Signal Transduction accepted a position as a Staff Scientist at the University of Massachusetts Medical School. His mentor was Stephen Shears.

Dr. Todd A. Jusko a fellow in the Epidemiology Branch accepted a position as an Assistant Professor in the Department of Public Health Sciences at the University of Rochester Medical Center, Rochester, NY. His mentor was Matt Longnecker.

Dr. Rajesh Kasiviswanathan a research fellow in the Laboratory of Molecular Genetics has accepted a position in the Purification Development Division at Fujifilm Diosynth Biotechnologies in Morrisville, N.C., a contract manufacturing organization that produces recombinant proteins, vaccines, and monoclonal antibodies using good manufacturing practices. His mentor was William Copeland.

Dr. Anne Lai a postdoctoral trainee in the Laboratory of Molecular Carcinogenesis has taken a position as a Translational R&D Principal Research Associate at Expression Analysis, a Quintiles company in Durham, NC. Her mentor was Paul Wade.

Dr. Qing Liu, a visiting fellow in the Laboratory of Toxicology and Pharmacology, has taken a postdoctoral position at Stanford University. His mentor was Jonathan Freedman.

Dr. Gang Lu, a postdoctoral fellow in the Laboratory of Structural Biology, has gone to Case Western Reserve University as a dental student. His mentor was Traci Hall.

Dr. Kyoko Okamoto, visiting fellow in the Laboratory of Respiratory Biology is leaving to take a position as Assistant Professor at the University of Nagasaki, Japan. His mentor was Anton Jetten.

Dr. Jacqueline de Marchena Powellm a postdoctoral fellow in the Laboratory of Neurobiology accepted a position as a Medical Science Writer/Editor for Education & Training Systems, International. Her mentor was Patricia Jensen.

Dr. Bhargavi Rao, an IRTA fellow in the Laboratory of Molecular Carcinogenesis has taken a position in regulatory affairs at Pharmaceutical Product Development (PPD). PPD is a global contract research organization providing services in the areas of drug discovery, development, and life cycle management. Her mentor was Trevor Archer.

Dr. Javier Revollo, a research fellow in the Laboratory of Signal Transduction, has accepted a two-year commissioners' fellowship program with the U.S. Food and Drug Administration (FDA). He was mentored by John Cidlowski and Xiaoling Li.

Dr. Douglas Ganini da Silva, a fellow in the Laboratory of Toxicology and Pharmacology, received the Larry Oberley Young Investigator Award from the Society of Free Radical Biology and Medicine. His mentor is Ronald Mason.

Dr. Ramendra Saha, a fellow in the Laboratory of Neurobiology, started a position as an Assistant Professor at the University of California in Merced. His mentor was Serena Dudek.

Dr. Jennifer Sims, a fellow in the Laboratory of Molecular Carcinogenesis, has taken a position as development research associate at Expression Analysis, a Quintiles company in Durham, NC. Her mentor was Paul Wade.

Dr. Jeffrey Stumpf, a research fellow in the Laboratory of Molecular Genetics has taken a position as a medical writer with MedThink SciCom in Raleigh, N.C. His mentor was William Copeland.

Dr. Fiona Summers, a visiting fellow in the Laboratory of Toxicology and Pharmacology, has taken a consultant position at PRIMA Consulting Group, Australia. Her mentor was Ronald Mason.

Dr. Darshini Trivedi, a fellow in the Laboratory of Toxicology and Pharmacology has taken a position as a clinical research scientist at Impact Pharmaceutical Services Inc. The company is a local contract research organization that specializes in providing regulatory and drug development consulting, medical writing, and project and program management to the pharmaceutical and biotech industries. Her mentor was Bob Langenbach.

Dr. Yan Wang, a postdoctoral fellow in the Epidemiology Branch has taken a position at Sterling Life Sciences, a CDC supports services contractor, as a programmer analyst doing HIV and sexually transmitted diseases work. Her mentor was Walter Rogan.

Dr. Danielle Watt, an IRTA Fellow in the Laboratories of Structural Biology and Molecular Genetics is currently doing a second postdoctoral fellowship with Dr. Andrei Chabes at Umeå University in Sweden. Her mentor was Thomas Kunkel.