



# Environmental Factor

Your Online Source for NIEHS News

November 2010

## NIEHS Spotlight



### [Birnbaum elected to Institute of Medicine](#)

NIEHS/NTP Director Linda Birnbaum, Ph.D., became one of five NIH leaders to be elected to the highly prestigious Institute of Medicine (IOM) of the National Academies.



### [Serena Dudek tenured](#)

Serena Dudek, Ph.D., head of the NIEHS Laboratory of Neurobiology Synaptic and Developmental Plasticity Group, received tenure from the National Institutes of Health Central Tenure Committee Oct. 21.



### [NIEHS selects 2011 ONES awardees](#)

Eight early-stage tenure-track investigators, who will receive 2010 NIEHS Outstanding New Environmental Scientist (ONES) awards, will visit the Institute to present seminars about their research projects.



### [Breast cancer advisory committee holds first meeting](#)

The Interagency Breast Cancer and Environmental Research Coordinating Committee (IBCERCC) held its inaugural meeting in Washington, D.C. Sept. 30-Oct. 1.

## Science Notebook



### [UNC researcher gives Falk Lecture](#)

Nutrition expert Steven Zeisel, M.D., Ph.D., discussed how diet and chemical exposures influence the requirement of choline in human development during the Hans L. Falk Memorial Lecture.



### [GEMS holds 28th annual fall meeting](#)

The Genetics and Environmental Mutagenesis Society (GEMS) held its annual meeting Oct. 15 at the Sheraton Imperial Hotel and Convention Center in Research Triangle Park, N.C.



### [NIEHS scientists at the 2010 NIH Research Festival](#)

Twenty-one NIEHS fellows were honored as winners of the 2010 Fellows Award for Research Excellence (FARE) at the National Institutes of Health Research Festival in Bethesda, Md.



### [New brain researcher to join NIEHS](#)

Douglas Caruana, Ph.D., currently a postdoctoral fellow in the United Kingdom, will join the Synaptic and Developmental Plasticity Group, led by Serena Dudek, Ph.D., as a visiting fellow in 2011.

## NIEHS Spotlight



### [Forum brings scientists and community together](#)

Residents from a neighborhood known as Rubbertown filled an auditorium in Louisville, Ky., to discuss concerns about possible links between emissions from local petrochemical factories and poor health.



### [NIEHS funds child health research centers](#)

NIEHS announced grants totaling \$54 million as part of a federal initiative to develop new research technologies and approaches to discover how the environment influences children's health.



### [Alma Mater honors Birnbaum](#)

The University of Illinois at Urbana-Champaign will honor NIEHS/NTP Director Linda Birnbaum, Ph.D., with the 2010 College of Liberal Arts & Sciences Alumni Achievement Award during its homecoming activities.



### [Remembering the people of Haiti](#)

J. Nadine Gracia, M.D., described the obstacles in restoring and improving health care in Haiti, particularly the educational and training infrastructure, in a recent talk at NIEHS.



### [NIEHS employees win Green Dream Team Award](#)

Four NIEHS staffers were honored with the Green Dream Team Award for their work on the Interagency Working Group (IWG) on Climate Change and Health.

## Science Notebook



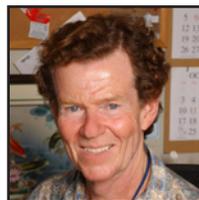
### [NIEHS/NTP postdocs win at NC SOT meeting](#)

NIEHS and NTP postdoctoral fellows dominated the competition for the President's Award for Research Competition at the North Carolina Regional Chapter of the Society of Toxicology (NC SOT) Fall Meeting.



### [Children, males, and blacks at increased risk for food allergies](#)

A new NIEHS-funded study estimates that 2.5 percent of the United States population, or about 7.6 million Americans, have food allergies, with rates higher for children, non-Hispanic blacks, and males.



### [Succimer found ineffective for removing mercury](#)

According to Walter Rogan, M.D., head of the Pediatric Epidemiology Group at the NIEHS, succimer — a drug used for treating lead poisoning — does not effectively remove mercury from the body.



### [This Month in EHP](#)

EHP dives into the topic of pools and health in this month's issue with two feature articles and a podcast about the risks and benefits of swimming in chlorinated pools.



### [Gary Aston-Jones presents next Distinguished Lecture](#)

Gary Aston-Jones, Ph.D., will continue the 2010-2011 Distinguished Lecture Series Nov. 23 at NIEHS by discussing the neuronal circuits that underlie motivated behavior and reward-based learning and memory.

## Inside the Institute



### [Feds aim high to support charities](#)

The 2010 Combined Federal Campaign (CFC) at NIEHS has its sights set on a record-setting year. If met, the Institute's goal of \$100,000 would be an all-time high.



### [NIEHS celebrates Hispanic heritage](#)

In celebration of Hispanic heritage month, the NIEHS Diversity Council invited Ileana Herrell, Ph.D., to talk about the history and contributions made by persons of Hispanic descent.

## Extramural Research

### [Extramural papers of the month](#)

- Cause of viox-induced cardiovascular events determined
- Promising target for Parkinson's disease treatment
- Prenatal PAH exposure lowers IQ

## Intramural Research

### [Intramural papers of the month](#)

- 3D structure of dust mite allergens
- DNA double-strand breaks may play a role in the mutagenesis of antibody diversification
- Genome instability due to ribonucleotide incorporation into DNA
- Effect of alteration in DNA methylation on lymphomas

## Calendar of Upcoming Events

- **Nov. 2** in Keystone 3003, 1:00-2:30 p.m. — Keystone Science Seminar Series with Arthur Grollman, M.D., topic TBA
- **Nov. 3** in Rodbell BC, 8:00 a.m.-5:00 p.m. — National Research Service Award (NRSA) Training Directors Meeting
- **Nov. 4** in Rodbell Auditorium, 8:00 a.m.-5:00 p.m. — NIEHS Science Awards Day
- **Nov. 6-10 (Offsite Event)** at the Colorado Convention Center in Denver, 8:00 a.m.-5:00 p.m. — American Public Health Association (APHA) [Annual Meeting and Exposition](#)
- **Nov. 6 (Offsite Event)** at the APHA Meeting and Exposition, 4:00-7:30 p.m. — The Division of Extramural Research and Training hosts the [Environmental Justice Forum](#)
- **Nov. 10-12 (Offsite Event)** at The Nines Hotel and Conference Center in Portland, Ore., 8:00 a.m.-5:00 p.m. — Superfund Research Program [Annual Meeting](#)
- **Nov. 14-17 (Offsite Event)** at the Hilton Lexington/Downtown in Lexington, Ky. — [6th Conference on Metal Toxicity and Carcinogenesis](#)
- **Nov. 15** in Rall F193, 10:00-11:00 a.m. — Laboratory of Signal Transduction Seminar Series presentation on “Functions of Store-operated Calcium Entry” by James Putney, Ph.D.
- **Nov. 15-16** in Rodbell Auditorium, 8:30 a.m.-3:45 p.m. — NIEHS Centers for Nanotechnology Health Implications Research (NCNHIR) Consortium Meeting
- **Nov. 16** in Keystone 1003AB, 10:00 a.m.-2:00 p.m. — Annual Health Fair
- **Nov. 16-18 (Offsite Event)** at the Roosevelt Hotel in New York — Breast Cancer and the Environment Research Program [Extended Environmental Exposures Annual Meeting](#)
- **Nov. 17** in Keystone 2164/2166, 10:00 a.m.-1:00 p.m. — Keystone Science Seminar Series with Andre Nel, M.D., speaking on “Nanotechnology”
- **Nov. 17-19** in Rodbell Auditorium, 8:00 a.m.-5:00 p.m. — Superfund Workshop on Microbiome-Xenobiotic Interactions
- **Nov. 18** in Rall B450, 10:00-11:00 a.m. — Laboratory of Molecular Carcinogenesis Seminar Series presentation on “Genome-wide Interactions Between the Transcription Machinery and Chromatin” by Frank Pugh, Ph.D.
- **Nov. 23** in Rodbell Auditorium, 11:00 a.m.-12:00 p.m. — Distinguished Lecture Series with Gary Aston-Jones, Ph.D., speaking on “Seeking Reward: Overdoing It with Orexin Neurons”
- View More Events: [NIEHS Public Calendar](#)

# NIEHS Spotlight

## Birnbaum elected to Institute of Medicine

By Eddy Ball

NIEHS/NTP Director Linda Birnbaum, Ph.D., became one of the newly elected members of the [Institute of Medicine \(IOM\) of the National Academies](#) Oct 1. She will join other new members of what is known as the IOM Class of 2011, during a formal welcome at the group's next annual meeting Oct. 16-17, 2011 (see text box).

In his notification to Birnbaum, IOM President Harvey Fineberg, M.D., Ph.D., pointed to Birnbaum's "professional achievement and demonstrated interest, concern, and involvement with problems and critical issues that affect the health of the public."

IOM's more than 1,700 members and foreign associates are distinguished scientists chosen from the ranks of government at all levels, educational institutions and non-profit organizations, and the private sector. IOM selects as many as 65 new members and up to five new foreign associates each year.

The IOM is an independent, nonprofit organization that works outside of government, to provide unbiased and authoritative advice to decision makers and the public. According to the IOM, more than 2,000 individuals, members, and non-members volunteer their time, knowledge, and expertise each year to advance the nation's health through the work of the IOM.

IOM asks and answers the nation's most pressing questions about health and health care in [reports](#) authored by committees of leading national and international scientists. The 2010 IOM reports highlight such topics as "The Future of Nursing," "Antibiotic Resistance," and "Breast Cancer and the Environment." Currently underway at the request of the U.S. government is "[The 1946-1948 Public Health Service STD Inoculation Study](#)," investigating the scientific and ethical issues surrounding this controversial chapter in the history of American medical research.

Established in 1970, the IOM is the health arm of the National Academy of Sciences, which was chartered under President Abraham Lincoln in 1863. Nearly 150 years later, the National Academy of Sciences has expanded into what is collectively known as the National Academies, which comprises the National Academy of Sciences, National Academy of Engineering, National Research Council, and IOM.

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*With her expertise in environmental public health and primary prevention, Birnbaum will add to the diversity of the IOM Class of 2011. (Photo courtesy of Steve McCaw)*

### NIH leaders join the Institute of Medicine

**Linda Birnbaum, Ph.D.**, director of the National Institute of Environmental Health Sciences (NIEHS)

**Jeremy Berg, Ph.D.**, director of the National Institute of General Medical Sciences (NIGMS)

**Ira Pastan, M.D.**, chief of the Laboratory of Cell Biology, Center for Cancer Research at the National Cancer Institute (NCI)

**Thomas Wellems, M.D., Ph.D.**, chief of the Laboratory of Malaria and Vector Research at the National Institute of Allergy and Infectious Diseases (NIAID)

**Carl Wu, Ph.D.**, chief of the Laboratory of Biochemistry and Molecular Biology, Center for Cancer Research at NCI

More detailed summaries are available in the [NIH press release](#).

# Serena Dudek tenured

*By Larry Lazarus*

The National Institutes of Health Central Tenure Committee granted tenure to Serena Dudek, Ph.D., Oct. 21. Dudek leads the [Synaptic and Developmental Plasticity Group](#) in the NIEHS Laboratory of Neurobiology headed by David Armstrong, Ph.D.

Armstrong said the decision to grant tenure was largely influenced by Dudek's discoveries linking electrical signaling and rapid gene expression in neurons, and the regulation of synaptic plasticity. Armstrong also emphasized Dudek's enthusiasm for collaborating with NIEHS staff. "She interfaces with all the other investigators in our branch," he said. "She is the scientific hub of the laboratory."

Dudek also received support from NIEHS Acting Scientific Director David Miller, Ph.D., who was delighted with the confirmation of her tenure, stating, "Serena is a bright and accomplished neurobiologist who has already made a name for herself."

Finding the proper sentiment to explain her feelings on getting tenure was difficult for Dudek. She admitted, "It's really gratifying that my colleagues find my research at a high enough caliber." Jokingly, she confessed that the prospect of moving to a new office with a window was frosting on the cake. Dudek hopes that tenure will also bring more space and resources for her research in the future.

Writing from Moscow, Natalia Bastrikova, Ph.D., Dudek's former research fellow from 2004 to 2009, emphasized three personality traits that make Dudek highly successful: innovative, open-minded, and supportive. She continued, "For her, science is never tight and defined facts. This is a journey into discovery."

Dudek's career researching synaptic plasticity has spanned almost 25 years. She began studying the topic as an undergraduate and, in 2010, received the A.E. Bennett Research Award from the Society of Biological Psychiatry for research by a young investigator.

## **Dudek outlined three directions for her ongoing studies**

The first concerns the pruning of excess synapses, which is critical for completing brain circuitry development. Based on her discovery that stimulating patterns induce long-term depression (LTD) in the hippocampus, she hypothesized and found that repeated LTD leads to synapse elimination. Dudek mentioned that she is currently investigating the molecular mechanisms underlying this structural change in brain circuitry.

A second project involves how neuronal activity rapidly regulates gene transcription. Excitedly, Dudek explained that several genes are up-regulated by experience within 5 minutes. Her group found evidence that action potentials are likely the trigger for this extremely fast gene regulation.

Finally, a specific set of neurons in area CA2 of the hippocampus is the topic of her third program. The hippocampus is part of the brain's limbic system, the seat of emotion and memory transfer, but plasticity in this particular area had never been studied. Growing evidence suggests that the CA2 is important for social behavior and is impaired in cases of bipolar disease and schizophrenia.



*Dudek said that NIEHS "funds me to do what I love to do most — science." (Photo courtesy of Steve McCaw)*

Based on the unique complement of neurotransmitter receptors and other molecules, Dudek predicts that the CA2 will play an important role in the pathology associated with autism spectrum disorders. Her work on CA2 has already led her to discover a new role by which caffeine exerts its effects and the remarkable role of the CA2-enriched “Homer Simpson gene (RGS14).”

Dudek’s studies permit insights into how environmental factors cause brain disease through its impact on neural circuitry. Her research succinctly fits the mission of the NIEHS, a vigorous supporter of her tenure application.

(Larry Lazarus, Ph.D. is a former principal investigator in the NIEHS Laboratory of Toxicology and Pharmacology. He is currently on detail as a writer for the Environmental Factor.)

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## NIEHS selects 2011 ONES awardees

*By Eddy Ball*

NIEHS announced funding for eight early-stage tenure-track investigators as 2010 Outstanding New Environmental Scientist (ONES) awardees. The highly competitive, five-year ONES grants will total approximately \$4 million for the first year, and the awardees, like their predecessors in the five-year-old program, will visit NIEHS to present talks about their research projects.

This year’s awardees are [Jason Bielas, Ph.D.](#), of the Fred Hutchinson Cancer Research Center and University of Washington; [Jared Brown, Ph.D.](#), of East Carolina University; [Sarah Delaney, Ph.D.](#), of Brown University; [Rebecca Fry, Ph.D.](#), of the University of North Carolina at Chapel Hill; former NIEHS postdoctoral fellow [Yu-Ying He, Ph.D.](#), of the University of Chicago; [Jill Poole, M.D.](#), of the University of Nebraska Medical Center; [Joseph Shaw, Ph.D.](#), of Indiana University; and [Alexander Star, Ph.D.](#), of the University of Pittsburgh.

Five of the new ONES awardees have training ties to NIEHS. As a postdoctoral fellow at NIEHS from 2001 to 2007, Yu-Ying He was part of the photobiology group headed by former Principal Investigator Colin Chignell, Ph.D. She later returned as a special volunteer in the free radicals group headed by Principal Investigator Ron Mason, Ph.D.

Shaw completed a fellowship at Dartmouth, working with NIEHS grantees Joshua Hamilton, Ph.D., Celia Chen, Ph.D., and Carol Folt, Ph.D. Delaney and Fry were postdoctoral fellows at the Massachusetts Institute of Technology, working with NIEHS grantees John Essigmann, Ph.D., and Leona Samson, Ph.D. Brown completed his Ph.D. at the University of Montana with NIEHS grantee Andrij Holian, Ph.D.



*Bielas plans to test his working hypothesis that the induction and accumulation of random mtDNA mutations fuels pathogenic mutant populations, aging, and age-related disease. He also intends to determine the molecular mechanisms of somatic mtDNA mutagenesis.*  
*Grant (Photo courtesy of Jason Bielas)*

Established in 2006, the ONES program identifies outstanding scientists who are in the early, formative stages of their careers and intend to make a long-term career commitment to research in the mission areas of NIEHS. The program assists them in launching an innovative research program focusing on problems of environmental exposures and human biology, human pathophysiology, and human disease.

“This grant is designed to serve as the foundation of a successful research career,” said NIEHS Training and Career Programs Health Scientist Administrator Carol Shreffler, Ph.D. “The program strives to build a long-term relationship between the awardees and NIEHS.”

“We indeed have made this a very competitive process,” Shreffler noted, “and we look forward to having these awardees make some very seminal contributions in the field of environmental health sciences.”



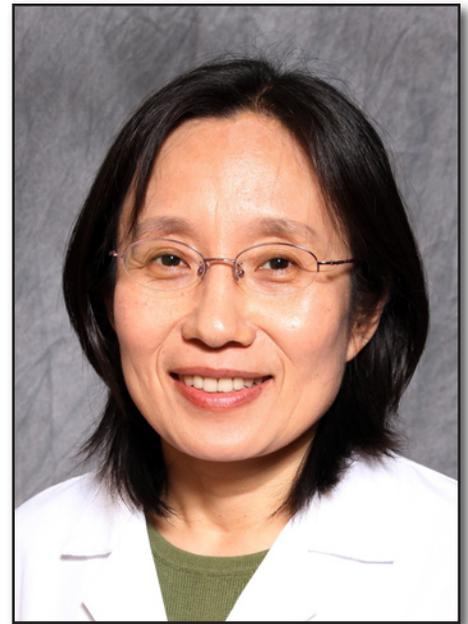
*Delaney seeks to define the mechanisms by which DNA damage, resulting from an inflammatory response or other environmental sources of damage, contributes to dynamic DNA mutations. Grant (Photo courtesy of Sarah Delaney)*



*Brown plans to pursue the hypothesis that carbon nanotube exposure activates mast cells through an IL-33 dependent mechanism, which results in pulmonary inflammation and adverse cardiovascular events due to the resultant release of inflammatory mediators. Grant (Photo courtesy of Jared Brown)*



*Studying a cohort of newborns in Mexico, Fry will investigate how exposure to arsenic alters newborn expression of the NF-kB inflammatory response pathway, and how this modulation is influenced by newborn genetics and epigenetics. Grant (Photo courtesy of Rebecca Fry)*



*Yu-Ying He intends to investigate the molecular mechanisms and consequences of ultraviolet radiation in the UVA band-induced phosphatase and tensin homolog down-regulation, as the molecular/cellular basis for the gene-environment interactions in the pathogenesis of skin cancer. Grant (Photo courtesy of Yu-Ying He)*



Poole will study how the pattern recognition receptors that are responsible for recognizing Gram-positive peptidoglycan — a polymer that surrounds bacteria — regulate the chronic inflammatory response to agricultural organic dust exposure. [Grant](#) (Photo courtesy of Jill Poole and the University of Nebraska Medical Center)



In his search for an effective method to remove toxic fibers of carbon nanotubes (CNTs) from the environment, Star will utilize enzymatic catalysis to initiate CNT degradation in environmentally and physiologically relevant settings. [Grant](#) (Photo courtesy of Joshua Franzos)



Shaw will lead studies that examine gene copy number variation in the lake and pond dwelling planktonic crustacean *Daphnia*, commonly called the water flea, which is one of a handful of model organisms approved by the NIH for biomedical research. [Grant](#) (Photo courtesy of Indiana University)

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## Breast cancer advisory committee holds first meeting

By Rachel Gross and Jennifer Collins

The Interagency Breast Cancer and Environmental Research Coordinating Committee (IBCERCC) held its inaugural meeting in Washington, D.C. Sept. 30-Oct. 1. The advisory committee, established by the National Institute of Environmental Health Sciences (NIEHS), in collaboration with the National Cancer Institute (NCI), is comprised of 19 voting members, including representatives of federal agencies; non-federal scientists, physicians, and other health professionals from clinical, basic, and public health sciences; and advocates for individuals with breast cancer.

### Committee members describe research, identify gaps

The meeting consisted of presentations from federal members describing their respective agency's breast cancer and environment research portfolio, including scientific advances and perceived research gaps and needs. [Paolo Boffetta, M.D.](#), deputy director of the Tisch Cancer Institute at the Mount Sinai School of Medicine also provided the committee with an overview of relevant international research.

In addition to the presentations, committee members led discussions focusing on areas of critical scientific importance, including the current understanding of breast cancer and environment, insights from the study of normal mammary gland development, windows of susceptibility to environmental agents, better models and exposure assessment tools, and research translation and community participation.

The committee developed a draft outline and defined three overarching themes that will guide the development of the IBCERCC Report:

1. State-of-the-Science: Defining “environment,” summarizing current knowledge of normal versus abnormal development and the etiology of breast cancer and multiple exposures across the lifespan, reviewing of federal research portfolio, and conceptualizing methods to put scientific opportunities and resources to use.
2. Research Process: Setting research priorities, reducing redundancies, process for soliciting research, developing collaborations, identifying issues with peer review and the most appropriate model systems for breast cancer and environment research
3. Research Translation, Dissemination, and Policy Implications: Encouraging community participation, determining when research is ready for dissemination to the public, and identifying best practices for research translation.



*DERT Interim Director Gwen Collman, Ph.D., serves as executive secretary of the IBCERCC. (Photo courtesy of Steve McCaw)*

### **The committee’s responsibilities**

The IBCERCC was created in October 2008, when the Breast Cancer and Environmental Research Act was signed into law, amending the Public Health Service Act.

The IBCERCC is charged with reviewing all research efforts within the U.S. Department of Health and Human Services (HHS) concerning the environmental and genomic factors related to the etiology of breast cancer, and developing a comprehensive summary of advances and recommendations regarding research gaps and needs for the Secretary of HHS.

The committee’s primary mission is to facilitate the efficient and effective exchange of information on breast cancer research among the member agencies, and to advise the NIH and other federal agencies in the solicitation of proposals for collaborative, multidisciplinary research, including proposals to further evaluate the environmental and genomic factors that may be related to the etiology of breast cancer. It will serve as a forum to assist in increasing public understanding of the member agencies’ activities, programs, policies, and research, and bring important matters of interest forward for discussion.

More information about the committee’s activities may be found on the [IBCERCC Web site](#).

(Jennifer Collins is a program analyst in the NIEHS Division of Extramural Research and Training (DERT) Susceptibility and Population Health Branch. Rachel Gross is a management analyst in the DERT Office of the Director.)

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*IBCERCC members Janice Barlow, left, and Sandra Haslam, Ph.D., discuss the meeting during a break. (Photo courtesy of Gwen Collman)*

# Forum brings scientists and community together

By Robin Arnette

Residents from a neighborhood known as Rubbertown filled an auditorium in Louisville, Ky., Oct. 20 to discuss concerns about possible links between emissions from local petrochemical factories and poor health. The community forum, sponsored by the University of Louisville [Center for Environmental Genomics and Integrative Biology \(CEGIB\)](#), an NIEHS core center, featured a panel of local and national leaders including [NIEHS/NTP Director Linda Birnbaum, Ph.D.](#), and representatives from the Rubbertown Emergency Action (REACT) network, the West Jefferson County Community Task Force, and the Louisville Metro Department of Public Health and Wellness.

For more information about the forum, please see the [University of Louisville press release](#).

During her opening remarks, Birnbaum said that Louisville had higher-than-average rates of obesity, asthma, diabetes, and cardiovascular disease, and that these numbers were highest in its African-American population. She suggested that the water and air quality in Louisville, and exposure to chemicals, may play a role in these illnesses.

“NIEHS spent roughly \$3 million right here in Louisville last year,” said Birnbaum. “This is important work that will help us answer questions about your environment and your health.”

Other experts in attendance maintained that poverty and socioeconomic factors were also involved in human health. They mentioned the difficulty in exercising in neighborhoods with no sidewalks or high crime, and eating healthy when more convenience stores dot the community.

Wave 3 News Sunrise anchor Jean West moderated the panel discussion, which included discussions about living downstream from the factories, concerns about exposures to multiple chemicals, and the best ways to improve communications between residents and industry management.

In addition to attending the forum, Birnbaum took part in other activities in Louisville including the 2010 Annual NIEHS Center Director’s Meeting Oct. 19-21 at CEGIB, and a bus tour of neighborhoods affected by the industrial plants. John Schelp, who coordinates community forums for NIEHS, also participated in the tour and witnessed the pervasiveness of chemicals firsthand.

“During the tour, emissions from smokestacks permeated the bus at times,” Schelp recalled. “We also passed a new middle school that was directly downwind of a large coal-burning power plant. A local scientist explained that the air-borne plume may eventually settle back to ground level at the school.”



More than 100 residents, scientists, and environmental advocates filled the Nia Center for the community forum. (Photo courtesy of John Schelp)



CEGIB Community Outreach Director Irma Ramos, M.D., left, and CEGIB Core Center Director Ken Ramos, Ph.D., participated in the panel along with Birnbaum. (Photo courtesy of Paul Jung)



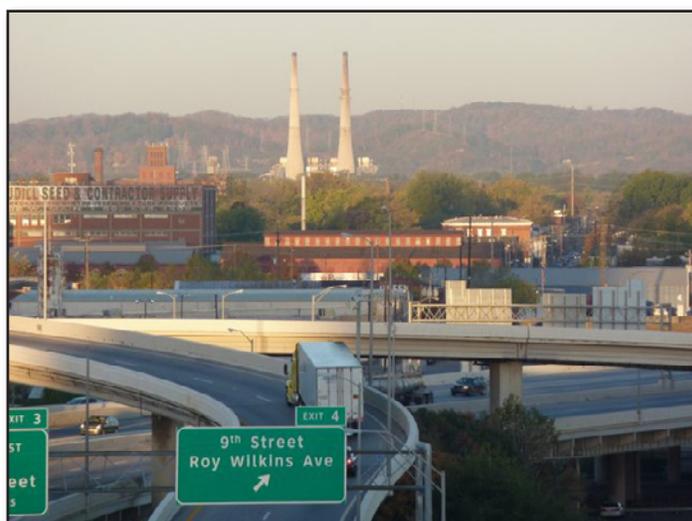
*Birnbaum talked with other panelists after the forum. (Photo courtesy of John Schelp)*



*West Louisville resident, Clifton David, asked the panel about health care access for his community. (Photo courtesy of John Schelp)*



*Birnbaum appeared with local television anchor Jean West on the Wave 3 News Sunrise soundstage. (Photo courtesy of Paul Jung)*



*Two smokestacks can be seen in the West Louisville skyline. (Photo courtesy of John Schelp)*

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## **NIEHS funds child health research centers**

*By Ed Kang*

NIEHS announced grants totaling \$54 million Oct. 20, as part of a federal initiative to develop new research technologies and approaches to discover how the environment influences children's health. The [program](#) of university-based research centers is supported by joint funding from NIEHS and the U.S. Environmental Protection Agency (EPA).

Focusing on exposure to environmental agents, such as pesticides, metals, air pollution, and endocrine disruptors, the 12 newly-funded Centers for Children's Environmental Health and Disease Research will engage

in a wide range of basic, applied, and community-based participatory research to better understand, and ultimately reduce, the burden of disease (see text box).

The program initially began in 1998 when NIEHS and EPA funded eight centers. In 2008, the two agencies asked for proposals to fund the next generation of centers. The resulting changes leverage the development of approaches utilizing cutting-edge assessment and biomonitoring tools, interaction with communities in the research process, and new disciplines such as epigenetics, which examine how exposure to chemicals and other environmental agents can cause genetic changes for several generations. Additionally, the new funding establishes formative centers, to conduct research where the link between children's health and the environment is not yet well-established, but may be stimulated by the creation of collaborative teams.



*Kimberly Gray, Ph.D., is a health scientist administrator in the NIEHS Susceptibility and Population Health Branch. She manages the pediatric epidemiology and community participatory research programs, and directs the NIEHS/EPA Centers for Children's Environmental Health and Disease Research program. (Photo courtesy of Steve McCaw)*

## Centers for Children's Environmental Health and Disease Research

### Children's Centers

- Patricia Buffler, Ph.D., University of California, Berkeley, Center for Integrative Research on Childhood Leukemia and the Environment
- Gregory Diette, M.D., Johns Hopkins University, Baltimore
- Brenda Eskenazi, Ph.D., University of California, Berkeley, Center for Children's Environmental Health Research
- Elaine Faustman, Ph.D., University of Washington, Seattle, Center for Child Environmental Health Risks Research
- Frederica Perera, Dr. P.H., Columbia University, New York City, The Columbia Center for Children's Environmental Health
- David Schwartz, M.D., National Jewish Health, Denver

### Formative Centers

- Kim Boekelheide, M.D., Ph.D., Brown University, Providence, R.I.
- Margaret Karagas, Ph.D., Dartmouth College, Hanover, N.H., Children's Environmental Health & Disease Prevention Research Center
- Karen Peterson, D.Sc., University of Michigan, Ann Arbor
- Susan Schantz, Ph.D., University of Illinois at Urbana-Champaign
- Ira Tager, M.D., University of California, Berkeley, Center for Environmental Public Health
- Tracey Woodruff, Ph.D., University of California, San Francisco

“This important research program exemplifies the federal government’s commitment to our most valuable resource, our children,” said Linda Birnbaum, Ph.D., director of NIEHS and the National Toxicology Program. “The unique interdisciplinary nature of the centers allows them to work closely with their communities to develop effective intervention strategies for at-risk populations.”

To promote collaboration and interaction, NIEHS and EPA brought staff from the 12 newly-awarded centers together with researchers from two existing programs. The meeting, which took place Oct. 18-20 in Washington, D.C., provided opportunities to share lessons learned and plan for future directions. Participants also focused on effective approaches for sharing research findings with the scientific community, parents, and the general public.

(Ed Kang is a public affairs specialist in the Office of Communications and Public Liaison and a regular contributor to the Environmental Factor.)

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## Alma Mater honors Birnbaum

*By Eddy Ball*

The University of Illinois at Urbana-Champaign will honor NIEHS/NTP Director [Linda Birnbaum, Ph.D.](#), with the 2010 College of Liberal Arts & Sciences (LAS) Alumni Achievement Award Oct. 22-23. The ceremony will take place during [homecoming](#) activities, as Illinois celebrates its 100th anniversary with LAS alumni and friends.

The [LAS](#) Alumni Achievement Award is given to the alumnus or alumna who, by outstanding achievement, has demonstrated the values derived from a liberal arts and sciences education. The award recognizes outstanding alumni for their professional achievement, creative achievement, worthy cumulative performance through the years, or recent acknowledgement by community or professional peers.



*In May, Birnbaum’s undergraduate alma mater awarded her an honorary doctorate, during commencement at the University of Rochester. (Photo courtesy of Steve McCaw)*

 **Linked video:**  
[Watch a tribute to LAS alumni \(0:30\)](#)  
(Launches in new window)

Download Media Player: 

Birnbaum joins a select group of distinguished graduates that includes eight Nobel Laureates and six Pulitzer Prize winners, out of a total of approximately 145,000 alumni. As a graduate student at the University of Illinois, Birnbaum earned an M.S. in microbiology, and completed her Ph.D. in microbiology with a minor in biochemistry, successfully defending her thesis, “Localization, Enrichment, and *in vitro* Transcription of Ribosomal RNA Genes in *Escherichia coli*,” in 1972.

In addition to the LAS Alumni Awards reception and dinner Oct. 22, Birnbaum was recognized at the LAS homecoming celebration the morning of Oct. 23. She was also invited to attend the annual homecoming game pitting the Illinois Fighting Illini against the Indiana University Hoosiers.

Homecoming at Illinois is the longest such continuously running collegiate event, beginning in 1910 and marking its 100th anniversary in 2010. The occasion has taken place in each of those 100 years, with the exception of 1918 when the event was canceled because of World War I.

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## Remembering the people of Haiti

*By Melissa Kerr*

The immediate crisis in Haiti may have passed, but according to guest speaker J. Nadine Gracia, M.D., Haitians face a colossal effort as they try to rebuild their health care infrastructure.

Gracia described the obstacles in restoring and improving health care in Haiti, particularly the educational and training infrastructure, in a talk Sept. 29 at NIEHS. NIEHS/NTP Director Linda Birnbaum, Ph.D., hosted the talk and welcomed Gracia to speak on “Rebuilding health professions education in Haiti.”

### Haiti in turmoil

A devastating magnitude 7.0 earthquake hit the most populated area of Haiti Tuesday, Jan. 12, 2010. The epicenter was near the town of Leogane, approximately 16 miles west of the capital city Port-au-Prince. The Haitian government reported that approximately 230,000 people died, 300,000 were injured and 1 million lost their homes. The estimated damage was \$7.7 billion, with \$11.5 billion in reconstruction costs. The destruction of hospitals, clinics, and medical training institutions jeopardized the future of the health care workforce in Haiti.

“The building that housed the Ministry of Health collapsed and was completely destroyed,” Gracia explained. “The sad part was that many of the people who would have been vital to rebuilding the country’s health care system perished in that collapse. The workers who were left had no place to work and very few colleagues to get the job done.”

### The U.S. helps its neighbor

Gracia said that President Obama reacted to the crisis by insisting there be a swift, but coordinated and aggressive effort across the federal government to help support the recovery efforts in Haiti. The National Disaster Medical System constituted the primary response, with several medical and surgical teams activated days after the earthquake. According to Gracia, they saw more than 30,000 patients, performed 167 surgeries, and delivered 45 babies. In addition, the U.S. Department of Health and Human Services (HHS), in partnership with the Haitian Ministry of Health, administered mass vaccinations to stave off potential epidemics of infectious disease.



*Gracia, above, serves as chief medical officer to the HHS Assistant Secretary for Health Howard Koh, M.D., M.P.H. (Photo courtesy of Steve McCaw)*

While some teams focused on helping the living, other teams concentrated on giving back dignity to the dead. Gracia added that the mortuary team faced a particularly daunting task of identifying victims, since Haiti lacked an established dental records system before the catastrophe.

### **The health care profession rebuilds**

Gracia maintained that one of the biggest challenges was just getting the debris out of the way. Although debris removal is still an ongoing issue, she said training institutions have asked for help in setting up tents, prefabricated buildings, or any kind of temporary structure that will allow health care students to return to class.

According to Gracia, several HHS-hosted meetings recently brought leaders together from American and Canadian academic institutions, as well as representatives from the Ministry of Health and Haitian medical schools, to discuss how to rebuild the medical education system. As a result, a national committee developed the North American Initiative to Rebuild Medical Programs in Haiti, an HHS-lead consortium that would govern the development of graduate medical education. The plan would cover rebuilding medical institutions, development of infrastructure, evaluation of curriculum, recruitment and training of professors, and development and integration of a public health program into medical education.

“My work in the Haiti recovery has not been work,” Gracia concluded. “My purpose is to work with both American and Haitian governments in order to move forward on the HHS proposal.”

(Melissa Kerr studies chemistry at North Carolina Central University. She is currently an intern in the NIEHS Office of Communications and Public Liaison.)

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*Many attended Gracia's talk, including Rear Admiral William Stokes, D.V.M., right, director of the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods Director; and William Suk, Ph.D., left, director of the Center for Risk and Integrated Sciences and Superfund Research Program. (Photo courtesy of Steve McCaw)*



*NIEHS/NTP Director Birnbaum moderated the question and answer session following the seminar. (Photo courtesy of Steve McCaw)*

# NIEHS employees win Green Dream Team Award

By Eddy Ball

Four NIEHS staffers were part of a group honored with one of the 2010 GreenGov Presidential Awards in a ceremony Oct. 7 in Washington, D.C. ([see White House press release](#)). The group was honored with the Green Dream Team Award for its work on the Interagency Working Group (IWG) on Climate Change and Health.

The IWG issued a white paper, “A Human Health Perspective on Climate Change” ([see story](#)), that was published by NIEHS and Environmental Health Perspectives in April. The paper inspired new funding opportunities by NIH to address the IWG’s findings ([see story](#)).



**Linked video:**  
[President Obama discusses the GreenGov initiative \(03:33\)](#)  
(Launches in new window)

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*Dilworth is overseeing the new NIH climate change and health grants inspired by the white paper. (Photo courtesy of Steve McCaw)*

Representatives of seven federal agencies collaborated as part of the IWG. NIEHS employees honored for their contributions to the IWG are former Senior Advisor Chris Portier, Ph.D., Program Analyst Kimberly Thigpen Tart, Health Scientist Administrator Caroline Dilworth, Ph.D., and former Intramural Research Training Award Fellow Julia Gohlke, Ph.D.

Portier, Thigpen Tart, and three of their IWG colleagues accepted the award on the team’s behalf, during the ceremony in the South Court Auditorium of the Eisenhower Executive Office Building. The awards ceremony was part of the [2010 GreenGov Symposium](#), Oct. 5-7.

The Green Dream Team Award honors achievement in one of six categories recognized by GreenGov. It specifically recognizes “exceptional leadership by an interagency green team to effectively place a federal sustainability idea into action.” The team selected must have demonstrated that collaboration efforts were integral to its success. The award underscores the importance of partnerships among different agencies, councils, boards, or other groups.



*Gohlke was a fellow in Portier’s group at NIEHS, prior to being awarded an American Association for the Advancement of Science (AAAS) Science and Technology Policy Fellowship in 2009. (Photo courtesy of Steve McCaw)*

The GreenGov Presidential Awards celebrate extraordinary achievement in the pursuit of President Obama’s Executive Order 13514 on Federal Leadership in Environmental, Energy, and Economic Performance.

In that Executive Order, Obama wrote, “In order to create a clean energy economy that will increase our Nation’s prosperity, promote energy security, protect the interests of taxpayers, and safeguard the health of our environment, the Federal Government must lead by example.”

The White House points to the federal government’s 1.8 million civilian employees, 500,000 buildings, and \$500 billion in annual purchasing power, as compelling reasons why it has an obligation to lead by example in the areas of environmental, energy, and economic performance.

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# Science Notebook

## UNC researcher gives Falk Lecture

By Robin Arnette

Nutrition research performed over the past several decades highlights how diet and chemical exposures influence the requirement of choline in human development. One of the scientists whose work played a prominent role in these studies is Steven Zeisel, M.D., Ph.D. Zeisel talked about his work during the annual Hans L. Falk Memorial Lecture Oct. 4 at NIEHS.

Setting the stage for his seminar, Zeisel explained that metabolic variation — the amount that humans differ from each other in metabolism — was vital to understanding why some people respond to a particular dose of a nutrient, while others don't.

“We originally thought that all people were the same when it came to metabolism,” Zeisel said, “but the new view from the last decade or so is that changes in our genetic code lead to metabolic changes.”

### Humans differ in the requirement for choline

According to Zeisel, humans need choline and get some of it by eating choline-rich foods, such as beef liver and eggs, but the nutrient is also made in the liver by phosphatidylethanolamine N-methyltransferase (PEMT). To determine if choline was truly necessary, Zeisel and his team fed volunteers bread that contained the recommended amount of choline, in the form of phosphatidylcholine, for 10 days. Afterward, the researchers gave the participants bread with trace amounts of choline and watched them for 42 days.

“If they got sick, we stopped immediately and gave them the choline bread back. If they didn't get sick, we let them continue the study,” Zeisel added. “During the choline-depleted phase, blood choline levels dropped, which was expected, but we also saw the development of a fatty liver.”



*Zeisel is a Kenan Distinguished University Professor in Nutrition at the University of North Carolina at Chapel Hill Gillings School of Global Public Health. He is also Director of the UNC Nutrition Research Institute in Kannapolis, N.C. (Photo courtesy of Steve McCaw)*



*Director Birnbaum thanked Zeisel for a wonderful seminar by presenting him with a gift of appreciation on behalf of the Institute. (Photo courtesy of Steve McCaw)*

It turns out, Zeisel continued, that phosphatidylcholine makes up the outer membrane of a particle that transports fat and cholesterol out of the liver. If a person can't make the particle, the fat accumulates. When Zeisel added choline back into their diet, the fat in their livers decreased.

Zeisel determined that 80 percent of men and postmenopausal women developed organ damage when deprived of choline, but only 44 percent of premenopausal women developed damage. He postulated that estrogen provided protection to young women. Zeisel strengthened his argument when he found that PEMT contained estrogen response elements in its promoter and was induced by estrogen.

Further studies revealed that the reason 44 percent of women were still getting sick was due to a misspelling that caused a mutation in the set of genes that adjusted the requirement for choline. This mutation affected their liver cells' ability to respond to estrogen and, as a result, the women needed choline in their diet.

### Rodent studies reveal more about choline

Work with several collaborators concluded that pregnant rats who received four times the amount of choline during the five days of gestation (Day 11–17), when the hippocampus or memory center of the brain develops, gave birth to pups that exhibited elevated memory performance. These rats performed exceptionally well on memory tests — remembering where food was placed — at 2.5, 14, and 26 months after birth and throughout adulthood, compared to rats with no extra choline during development.

Zeisel ended his talk by discussing an environmental agent that interfered with choline. He and his team applied a high dose of diethanolamine (DEA), an additive in sunscreens and shampoos, to the skin of pregnant rodents for five days. Doing so lowered choline concentrations in the mothers' livers. DEA also reduced the amount of hippocampal cell division by half and increased the level of cell death in the pups *in utero*.

“DEA is about one or two percent of sunscreens and shampoos, and consumers are probably only getting 10 percent of the exposure in our study,” Zeisel urged, “but we don't know what effect these low exposures would have on women who use these products for nine months or a lifetime. The European Union has banned DEA in sunscreens and shampoos.”

NIEHS/NTP Director Linda Birnbaum, Ph.D., hosted this year's Falk Lecture and presented Zeisel with a gift of appreciation following the seminar.

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*Acting NIEHS Scientific Director and head of the Intracellular Regulation Group David Miller, Ph.D., was especially interested in Zeisel's liver studies. The liver is one of the organs Miller uses to study xenobiotic transport. (Photo courtesy of Steve McCaw)*



*The family of Hans L. Falk, for whom this lecture series is named, posed with the Institute director and seminar speaker. From left to right are Stephen Falk, Birnbaum, Gabrielle Falk, Zeisel, and Raymond Falk. (Photo courtesy of Steve McCaw)*

# GEMS holds 28th annual fall meeting

*By Thaddeus Schug*

The Genetics and Environmental Mutagenesis Society (GEMS) held its annual meeting Oct. 15 at the Sheraton Imperial Hotel and Convention Center in Research Triangle Park, N.C. The theme of this year's meeting was "Deep Sequencing, Regulation, and Cancer." There were nine poster presentations and five talks by talented students, trainees, and junior investigators competing for awards ([see text box](#)).

The meeting opened with introductory remarks by GEMS President [Jef French, Ph.D.](#), an NIEHS staff scientist and acting chief of the National Toxicology Program Host Susceptibility Branch. The agenda featured an afternoon of invited lectures on the development of new sequencing methodologies in genetics, and the information these new technologies reveal in molecular and cancer biology.

Moderating the meeting was GEMS President-elect Steve Little, a chemist and acting quality assurance manager with the National Center for Computational Toxicology at the Environmental Protection Agency (EPA). Little began his presentation by noting that "the deep sequencing in the title [of the meeting] refers to the multiple layers of genetic information, as well as the complete sequence information that is afforded by the newly developing high throughput technologies." He pointed out that whole genome sequencing may reveal clues to understanding the regulation of dynamic biological processes, such as cancer and developmental biology.

Assistant professor and director of the University of North Carolina at Chapel Hill (UNC) High Throughput Sequencing Facility Piotr Mieczkowski, Ph.D., gave the meeting's first keynote talk on "Next Generation Sequencing Tools." "I will not be talking about science, I will be talking about technology," said Mieczkowski, as he highlighted the rapid development of the next generation of sequencing tools. He noted that the newly emerging sequencing platforms allow investigators significantly more coverage of the genome, at a fraction of the original cost.

The next talk featured UNC School of Medicine assistant professor Ian Davis, M.D., Ph.D., who spoke on "Whole Genome Analysis of Transcriptional Regulation of Cancer." Davis explained how he has applied the functional aspects of genomic technologies to unravel the genetic mechanisms associated with a highly malignant form of cancer called Ewing sarcoma.



*North Carolina State University graduate student, Sam Suarez, spoke with NIEHS postdoctoral fellow Jana Stone, Ph.D., about her research on DNA damage caused by UV radiation. The poster session offered trainees and junior investigators additional opportunities to share their research with colleagues. (Photo courtesy of Steve McCaw)*



*Mieczkowski, left, and Davis, who were featured speakers in the morning session, took a break for refreshments. (Photo courtesy of Steve McCaw)*



*Keene has made use of gene sequencing for several important discoveries in RNA stability and translation. (Photo courtesy of Steve McCaw)*

Davis explained that Ewing sarcoma is caused by an aberrant chromosomal translocation that results in the formation of an oncogenic fused gene. He employs genome-wide analysis to study transcription and regulation of the hybrid gene. “Through the identification of oncogenic transcriptional mechanisms and relevant transcriptional targets, we hope to develop novel biologically-based therapies for these cancers,” said Davis.

The meeting’s final invited speaker was Jack Keene, a James B. Duke Professor in the Department of Molecular Genetics and Microbiology at Duke University, whose talk was titled, “Whole Genome Analysis of Transcription Regulation and Cancer.” Keene, who also chairs the NIEHS Board of Scientific Counselors, began his talk with an overview of his work that lead to the proposal of a new model of gene expression in eukaryotic cells that is based upon the regulation of RNA transcription by specific binding proteins (RBPs).

Keene went on to explain that, although RBPs appear to coordinate many key decisions during cell growth and differentiation, the dynamic changes during RNA translation are challenging to understand. Keene is currently using quantitative probability methods to predict RNA dynamics. He said, “The hope is that we can use these methods to quantify gene-disease phenotypes that can be used to identify small molecule drugs to target regulatory networks.”

(Thaddeus Schug, Ph.D., is a postdoctoral research fellow in the NIEHS Laboratory of Signal Transduction and a regular contributor to the Environmental Factor. He is currently on detail as a program analyst in the NIEHS Division of Extramural Research and Training.)

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*Little, right, posed with NIEHS postdoctoral fellow Steven Roberts, Ph.D., who was winner of the best oral presentation. (Photo courtesy of Steve McCaw)*

## GEMS winners

GEMS devoted more than half of its annual fall meeting toward showcasing the research accomplishments of young scientists. Winners typically use their grants for attending professional meetings.

### **Best Poster Presentation Awards (\$250 each):**

- Student Winner: Chris Sproul, “Mechanisms Underlying Sunlight-Induced Skin Carcinogenesis.” Sproul is a doctoral student in the UNC Toxicology program.
- Technician Winner: Lisa Smeester, “Altered DNA Methylation Patterns in Individuals with Arsenicosis.” Smeester is a technician in the lab of Rebecca Fry at UNC.
- Postdoctoral Winner: Amy Abdulovic, Ph.D., “Mechanisms of Mutagenesis *in vivo* due to Imbalanced dNTP Pools.” Abdulovic is a postdoctoral fellow in NIEHS Laboratory of Molecular Genetics DNA Replication Fidelity Group.

### **Best Oral Presentation Award (\$1500):**

- Steven Roberts, Ph.D., “Localized Hyper-mutability Caused by Chronic Alkylation Damage to a Eukaryotic Genome.” Roberts is a postdoctoral fellow in the NIEHS Laboratory of Molecular Genomics Chromosome Stability Group.

# NIEHS scientists at the 2010 NIH Research Festival

By Eddy Ball



NIEHS scientists and trainees joined their colleagues from across the National Institutes of Health (NIH) at the [2010 NIH Research Festival](#). They participated as chairs and presenters in five scientific symposia ([see text box](#)) and gave 20 poster presentations at the annual event Oct. 5-8 on the NIH campus in Bethesda, Md.

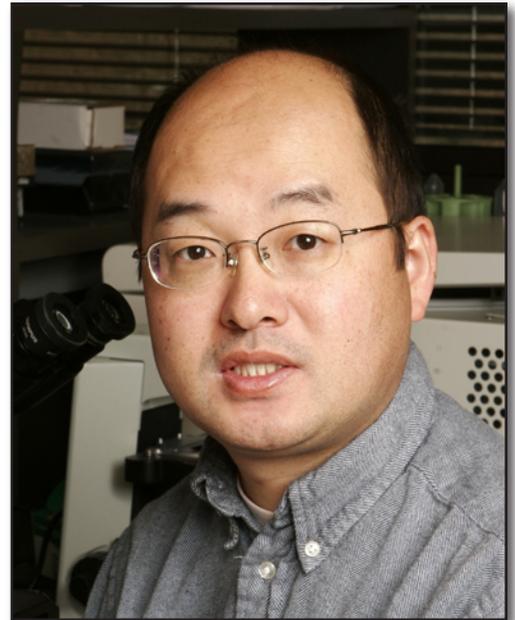
Twenty-one NIEHS fellows were honored as winners of the 2010 Fellows Award for Research Excellence (FARE) at the 14th annual FARE program and award ceremony ([see related story](#)). The annual competition selects the top 25 percent of abstracts reviewed by 56 different review panels. Winners receive \$1,000 travel awards for attendance at scientific meetings in their respective fields.

Along with poster presentations, two NIEHS fellows were selected to present talks at the Festival's symposia. This special recognition of excellence was bestowed upon FARE winner Sailu Yellaboina, Ph.D., for his study, "Identification of Novel Regulators Required for Embryonic Stem Cell Maintenance," and FARE winner Hideki Nakano, Ph.D., for his study, "Th2 Responses to Inhaled Antigens are Selectively Induced by Lung Resident CD103+ Dendritic Cells."

Yellaboina is a visiting fellow in the laboratory of Principal Investigator Raja Jothi, Ph.D. Nakano is a research fellow in the laboratory of Principal Investigator Donald Cook, Ph.D.

The Festival also featured opening remarks by NIH Director Francis Collins, M.D., Ph.D., an opening plenary session on "DNA Unwound: The Path from Characterization to Treatment of Rare and Common Genetic-based Disorders," and a two-day vendor exhibit.

The event culminated with a neurobiology symposium and tribute to [Marshall Nirenberg, Ph.D.](#), National Heart, Lung, and Blood Institute senior research biochemist and chief of the Laboratory of Biochemical Genetics who died in January at age 82. In 1968, Nirenberg shared the Nobel Prize in Physiology or Medicine for deciphering the genetic code.



*Nakano also won a FARE last year for his abstract on "The Impact of Surface ALDH1a2 on Pulmonary Dendritic Cells for Generation of Regulatory T Cells Leading to Immunotolerance to Inhaled Antigens."*  
(Photo courtesy of Steve McCaw)



*2010 FARE winner Sailu Yellaboina*  
(Photo courtesy of Steve McCaw)

## NIEHS scientists and FARE winners participating in symposia

- **Epigenetics, Chromatin, and Gene Regulation**, co-chaired by Principal Investigator Raja Jothi, Ph.D., with presentations on “Epigenetics of a Human Immune Response,” by Principal Investigator Paul Wade, Ph.D., and “esBAF Conditions the Pluripotent Genome for LIF/STAT3 Signaling by Opposing Polycomb,” by Jothi.
- **Metabolic Syndrome to Liver Regeneration and Cancer: Stem Cells**, with a presentation on “Identification of Novel Regulators Required for Embryonic Stem Cell Maintenance,” by visiting fellow and FARE winner Sailu Yellaboina, Ph.D.
- **Use of Molecular Profiles and Biomarkers in Translational Research**, with a presentation on “Proteomic and Gene Expression Arrays Suggest Common Altered Pathways in Multiple Autoimmune Diseases,” by Bethesda-based biologist Terrance O’Hanlon, Ph.D.
- **Getting “Energetic” about Mitochondrial Proteomics**, with presentations on “Palmitoylproteomic Profiling of the Macrophage Identifies a Role for Palmitoylation in Mitochondrial Targeting of Phospholipid Scramblase 3,” by Principal Investigator Michael Fessler, M.D., and “Disease Variants of the Human Mitochondrial DNA Helicase Encoded by C10orf2 Differentially Alter Protein Stability, Nucleotide Hydrolysis, and Helicase Activity,” by staff scientist Matthew Longley, Ph.D.
- **Asthma: From Bench-to-Bedside**, co-chaired by Acting Clinical Director Darryl Zeldin, M.D., with presentations on “Th2 Responses to Inhaled Antigens are Selectively Induced by Lung Resident CD103+ Dendritic Cells,” by research fellow and FARE winner Hideki Nakano, Ph.D., “Hyaluronic Acid and Asthma: A New Therapeutic Target?” by Principal Investigator Stavros Garantziotis, M.D., and “Novel Effects of Dyslipidemia in Airway Inflammation and Asthma Pathogenesis,” by Fessler.

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## New brain researcher to join NIEHS

*By Emily Zhou*

Douglas Caruana, Ph.D., currently a postdoctoral fellow with Zafar Bashir, Ph.D., at the Medical Research Council Center for Synaptic Plasticity at the University of Bristol in the United Kingdom, spoke at NIEHS Oct. 1 as part of the [Laboratory of Neurobiology](#) weekly seminar. As it turned out, the talk became an on-site interview for Caruana to pursue a visiting fellow position in the [Synaptic and Developmental Plasticity Group](#), led by Serena Dudek, Ph.D.

“I was very pleased with his profound expertise and broad knowledge in medial prefrontal cortex (mPFC) and other brain regions, so I offered him the position very quickly,” Dudek said excitedly. “His expertise fits very well into what we want to investigate, and we believe having him here will benefit our group profoundly.”

Caruana accepted the offer, and he will join the NIEHS team sometime in January 2011. Because so little is known about functions of the hippocampal *Cornu Ammonis 2* (CA2) region of the brain, Dudek’s group plans to explore the role of CA2 in memory formation and social behavior. Previous work from other labs using CA2-enriched gene knock outs resulted in either memory enhancement or deficits in social behavior. The finding led Dudek to speculate that CA2 plays a role in autism.

“With [Caruana] on board, our research will progress forward in CA2 functions,” she added. “No doubt, this new addition will pump in fresh blood for neuroscience research at NIEHS.”

### **Object-in-place associative memory**

Caruana is an expert electrophysiologist who works with both *in vivo* and *in vitro* preparations of rat parahippocampal and neocortical areas. He uses field potential recordings in conscious and anesthetized rats, as well as whole-cell current- and voltage-clamp recordings in brain slices, to investigate the cellular mechanisms underlying memory storage.

His seminar titled “Everything in its right place: A role for long-term synaptic depression in the formation of object and place associations,” opened with a picture of a room filled with different objects occupying specific spatial locations. He asked the audience, “How do we know what objects are there and where they are placed?” Caruana explained that the “what” information is controlled by the perirhinal cortex of the brain, and the “where” information is mediated by the hippocampus.

“Forming associations between objects and places is thought to be mediated by the mPFC, and mPFC receives prominent input from the hippocampus and perirhinal cortex, thereby forming a neural circuit which plays an important role in memory and learning,” Caruana explained. He and others in the field hypothesized that changes in synaptic strength in the mPFC may underlie the formation of object and place associations.

### **Molecular mechanism**

According to Caruana, cholinergic innervation of the mPFC has been implicated in many cognitive functions and pathological conditions. Using whole cell voltage clamp recordings of intracellular excitatory postsynaptic currents, he identified a form of long-term synaptic depression mediated by activation of muscarinic acetylcholine receptors and activity of protein kinase C.

Changes in cholinergic transmission may play a critical role in the formation of object and place associations, by inducing lasting plasticity in the mPFC. He said that combined behavioral and electrophysiological studies will examine whether acetylcholine-dependent synaptic depression is involved in the formation of object and place associations.

(Emily Zhou, Ph.D., is a research fellow in the NIEHS Laboratory of Signal Transduction Inositol Signaling Group.)

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*From left to right are Dudek, Caruana, and Maile Henson, Ph.D., a postdoctoral fellow currently working in Dudek's group.  
(Photo courtesy of Steve McCaw)*

# NIEHS/NTP postdocs win at NC SOT meeting

By Eddy Ball

NIEHS and NTP postdoctoral fellows dominated the competition for the President's Award for Research Competition at the [North Carolina Regional Chapter of the Society of Toxicology \(NC SOT\)](#) Fall Meeting Oct. 7 at NIEHS. The first order of business at the annual event was presentation of awards before a near-capacity audience that included NIEHS/NTP Director Linda Birnbaum, Ph.D., and many members of the NTP, along with members from other organizations involved in toxicology.

As first place winner, visiting fellow Yuanyuan Xu, M.D., Ph.D., received a cash award of \$500 and the opportunity to give a 20-minute presentation of her research at the meeting. Xu is a member of the National Toxicology Program Cellular and Molecular Pathology Branch, headed by research pharmacologist Michael Waalkes, Ph.D. She was first author on a study titled "Epithelia Malignantly Transformed by Arsenic or Cadmium Drives Nearby Normal Stem Cells Towards a Malignant Phenotype," with co-authors Erik Tokar, Ph.D., and Waalkes.

With her second-place win, visiting fellow Yang Sun, Ph.D., received a cash award of \$250 and recognition by NC SOT. Sun is also a member of the Waalkes group. She is first author on a study titled "Overabundance of Putative Cancer Stem Cells in Human Skin Keratinocyte Cells Malignantly Transformed by Arsenic."

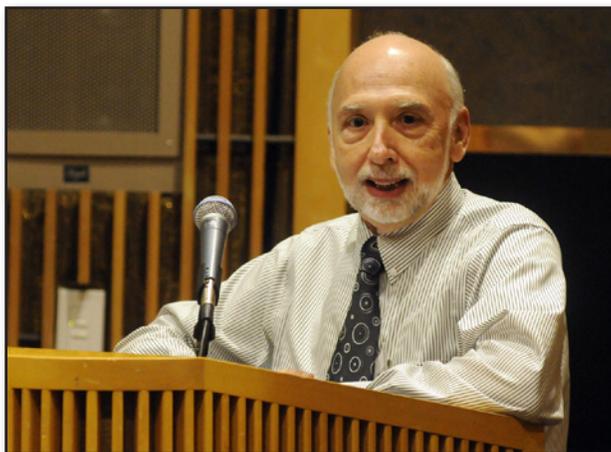
The third place winner is Visiting Fellow Zhengyu Yin, Ph.D., a member of the NIEHS Cell Biology Group headed by Principal Investigator Anton Jetten, Ph.D. Yin received a cash of award of \$100 for his paper titled "RAP80 Plays a Critical Role in Maintaining Genomic Stability." Jetten was a coauthor.

The NC SOT meeting was organized around the theme of "Bioengineered Cellular and Animal Models for Toxicology." Following a presentation by first place winner Xu, attendees heard talks by senior scientists on the leading edge of bioengineering:

- "Humanized Mice as Tools for Basic and Translational Research" by [Victor Garcia-Martinez, Ph.D.](#), of the University of North Carolina at Chapel Hill Center for AIDS Research. According to Garcia-Martinez, inoculating immune system knock out mice with



*Melanie Foster, the 2010-2011 president of the NC SOT, presided over the meeting and awards ceremony. (Photo courtesy of Steve McCaw)*



*The current vice president of the NC SOT, Darol Dodd, organized the meeting and introduced the speakers. (Photo courtesy of Steve McCaw)*



*Victor Garcia-Martinez (Photo courtesy of Steve McCaw)*

human stem cells allows researchers to exactly replicate the human phenotype in response to HIV infection, transmission, and treatment in efforts to test safety and efficacy of treatments and aid in drug development.

- “How to Make a Liver for Dummies” by Pedro Baptista of the [Wake Forest Institute for Regenerative Medicine](#). Baptista discussed efforts underway to use cell therapy to replace damaged urinary bladder tissue or implant a device in the body to take over liver function. These methods help address the shortage of donated organs for transplantation and increase available options in the treatment of traumatic and battlefield injuries.

With 322 members, NC SOT is one of the largest regional chapters of SOT. It is preparing a regional chapter poster and time capsule as part of the 50th anniversary celebration of SOT next March in Washington, D.C.



The NC SOT president congratulated the NIEHS/NTP postdocs on their exceptional research this year. From left to right are Foster, Yin (third place), Sun (second place), and Xu (first place). (Photo courtesy of Mike Hughes, EPA)



Pedro Baptista (Photo courtesy of Steve McCaw)

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## Children, males, and blacks at increased risk for food allergies

By Robin Mackar

A new NIEHS-funded study estimates that 2.5 percent of the United States population, or about 7.6 million Americans, have food allergies. Food allergy rates were found to be higher for children, non-Hispanic blacks, and males, according to the researchers. The odds of male black children having food allergies were 4.4 times higher than others in the general population.

The research, which appears in the *Journal of Allergy and Clinical Immunology*, is the first to use a nationally representative sample, as well as specific immunoglobulin E (IgE) or antibody levels to quantify allergic sensitization to common foods, including peanuts, milk, eggs, and shrimp. The hallmark of food allergy is production of IgE antibodies to a specific food protein. Once IgE antibody is made, further exposure to the food triggers an allergic response. IgE levels are often high in people with allergies.

“This study is very comprehensive in its scope. It is the first study to use specific blood serum levels and look at food allergies across the whole life spectrum, from young children aged 1 to 5, to adults 60 and older,” said [Darryl Zeldin, M.D.](#), acting clinical director at NIEHS and senior author on the paper. “This research has helped us identify some high risk populations for food allergies.” In addition to the identification of race, ethnicity, gender, and age as risk factors for food allergies, the researchers also found an association between food allergy and severe asthma.

Food allergy rates were highest (4.2 percent) for children 1 to 5 years. The lowest rates (1.3 percent) were found in adults over the age of 60. The prevalence of peanut allergies in children aged 1 to 5 was 1.8 percent, and in children aged 6 to 19 it was 2.7 percent. In adults, the rate was 0.3 percent.

The odds of patients with asthma and food allergies experiencing a severe asthma attack were 6.9 times higher than those without clinically defined food allergies.

“This study provides further credence that food allergies may be contributing to severe asthma episodes, and suggests that people with a food allergy and asthma should closely monitor both conditions and be aware that they might be related,” said [Andrew Liu, M.D.](#), of National Jewish Health and the University of Colorado School of Medicine, Denver, and lead author on the paper.

The data used for the study comes from the National Health and Nutrition Examination Survey (NHANES) 2005-2006. NHANES is a large nationally representative survey conducted by the National Center for Health Statistics, a part of the Centers for Disease Control and Prevention.

Zeldin and Liu note more research is needed to understand why certain groups are at increased risk for food allergy. The authors comment in the paper that food allergies may be under-recognized in blacks, males, and children, because previous studies relied on self-reporting and not food-specific serum IgE levels.

“Having an accurate estimate of the prevalence of food allergies is helpful to public health policy makers, schools and day care facilities, and other care providers, as they plan and allocate resources to recognize and treat food allergies,” said Linda Birnbaum, Ph.D., NIEHS/NTP director.

*Citation:* [Liu AH](#), [Jaramillo R](#), [Sicherer SH](#), [Wood RA](#), [Bock SA](#), [Burks AW](#), et al. National prevalence and risk factors for food allergy and relationship to asthma: Results from the National Health and Nutrition Examination Survey 2005-2006. *J Allergy Clin Immunol* 126(4):798-806.e13.

(Robin Mackar is the News Director in the NIEHS Office of Communications and Public Liaison and a regular contributor to the Environmental Factor)

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*Zeldin, who also heads the NIEHS Environmental Cardiopulmonary Disease Group, is a specialist in pulmonary critical care medicine. (Photo courtesy of Steve McCaw)*



*Liu is an associate professor in the National Jewish Health Department of Pediatrics and a specialist in pediatric allergic and immunologic conditions. (Photo courtesy of Andrew Liu)*

# Succimer found ineffective for removing mercury

By Robin Mackar

According to [Walter Rogan, M.D.](#), head of the Pediatric Epidemiology Group at the NIEHS, succimer — a drug used for treating lead poisoning — does not effectively remove mercury from the body. Rogan is a co-author on the paper that appears [online](#) in the *Journal of Pediatrics*.

“Succimer is effective for treating children with lead poisoning, but it does not work very well for mercury,” Rogan said. “Although it is not approved by the Food and Drug Administration to reduce mercury, succimer is reportedly being used for conditions like autism, in the belief that these conditions are caused, in part, by mercury poisoning. Our new data offers little support for this practice.”

Most mercury exposure in the United States is from methylmercury, found in foods such as certain fish. Thimerosal, a preservative that was once more commonly used in vaccines, contains another form of mercury, called ethylmercury.

Although researchers found that succimer lowered blood concentrations of mercury after one week, continued therapy for five months only slowed the rate at which the children accumulated mercury. The safety of higher doses and longer courses of treatment has not been studied.

## An earlier study provides the data

To conduct the study, the researchers used samples and data from an earlier clinical trial, led by NIEHS, called the [Treatment of Lead-exposed Children \(TLC\) trial](#). In the TLC study, succimer lowered blood lead in 2-year-old children with moderate to high blood lead concentrations.

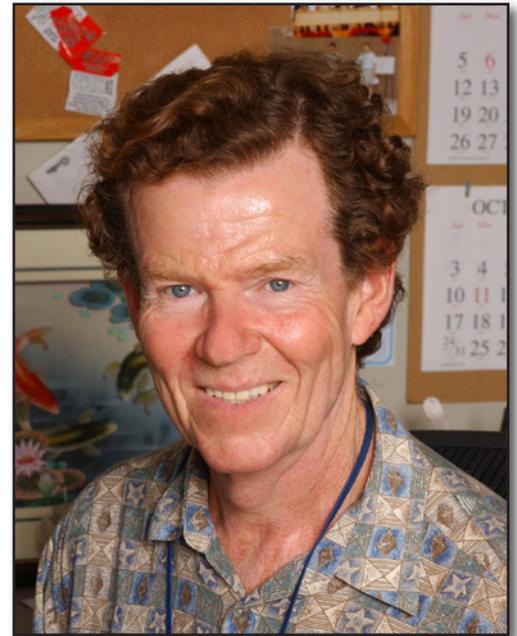
Using blood samples from 767 children who participated in the TLC trial, the researchers found that mercury concentrations were similar in all children before treatment and that during treatment, concentrations eventually increased in both groups, but more slowly in the children given succimer.

“Although succimer may slow the increase in blood mercury concentrations, such small changes seem unlikely to produce any clinical benefit,” Rogan explained. He and his colleagues had reported in an earlier paper that succimer has few adverse side effects, mostly rashes, and an unexplained increase in injuries in children given succimer rather than placebo.

The subjects of the study did not have unusually high blood mercury concentrations for African-American children, and the study did not investigate where the mercury in the children came from.

## Results are important for children’s health

“This research fills a gap in the scientific literature that could not be addressed any other way. We were fortunate to have samples already collected from toddlers who had been treated with succimer for lead poisoning,



*Rogan, who heads the Pediatric Epidemiology Group, studies the effects of environmental chemicals on the growth and development of children. (Photo courtesy of Steve McCaw)*

allowing us to help answer this important question,” said Linda Birnbaum, Ph.D., director of NIEHS and the National Toxicology Program.

Birnbaum noted NIH’s commitment to supporting research that provides critically needed information that will help drive more prevention and treatment options for children with autism and other neurodevelopmental disorders.

The study was supported by the NIEHS Intramural Research Program, the National Institute for Minority Health and Health Disparities at NIH, and the National Center for Environmental Health at the Centers for Disease Control and Prevention. The succimer, Chemet, and the placebo, were gifts from McNeil Laboratories, Fort Washington, Pa.

*Citation:* Cao Y, Chen A, Jones RL, Radcliffe J, Dietrich KN, Caldwell KL, et al. 2010. Efficacy of succimer chelation of mercury at background exposures in toddlers: a randomized trial. J Pediatr. Epub ahead of print. DOI:10.1016/j.jpeds.2010.08.036.

(Robin Mackar is the News Director in the NIEHS Office of Communications and Public Liaison and a regular contributor to the Environmental Factor.)

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## This Month in EHP

The November issue of [Environmental Health Perspectives \(EHP\)](#) dives into the topic of pools and health. The feature news article, “Swimmer, Protect Thyself: Cleaning Up the Pool Environment,” focuses on the uniform code of pool management in development by the Centers for Disease Control and Prevention (CDC), and discusses what swimmers can do to make pools safer. The other news feature, “The Perception Factor: Climate Change Gets Personal,” examines how the general public responds to climate change information.

In this month’s [podcast](#), host Ashley Ahearn speaks with Manolis Kogevinas, co-director of the [Centre for Research in Environmental Epidemiology](#) in Barcelona, Spain, about the risks and benefits of swimming in chlorinated pools.

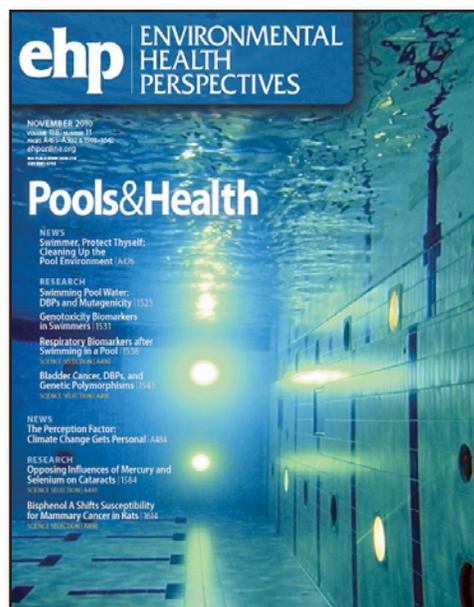
Among the research studies included in this issue are:

- Swimming Pool Water: DBPs [Disinfecting Byproducts] and Mutagenicity
- Genotoxicity Biomarkers in Swimmers
- Respiratory Biomarkers after Swimming in a Pool
- Bladder Cancer, DBPs, and Genetic Polymorphisms
- Opposing Influences of Mercury and Selenium on Cataracts
- Bisphenol A Shifts Susceptibility for Mammary Cancer in Rats

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<http://twitter.com/ehponline>



# Gary Aston-Jones presents next Distinguished Lecture

*By Angelika Zaremba*

Gary Aston-Jones, Ph.D., will continue the 2010-2011 Distinguished Lecture Series Nov. 23 at NIEHS by presenting “Seeking reward: Overdoing it with orexin neurons.” Patricia Jensen, Ph.D., a principal investigator in the Laboratory of Neurobiology, will host the seminar.

[Aston-Jones](#) is the Murray Chair of Excellence in Neuroscience, and director of the Center for Cognitive Neuroscience at the Medical University of South Carolina (MUSC) in Charleston, S.C. He is also co-director of the MUSC Neuroscience Institute, where the primary focus is to support and develop campus-wide interdisciplinary neuroscience activities and help bridge the gap between basic and clinical science.

The Aston-Jones [lab](#) focuses on neuronal circuits that underlie motivated behavior and reward-based learning and memory. One of the group’s interests is to identify the role of neuropeptide transmitters called orexins, also known as hypocretins, which are made exclusively in the hypothalamus.

His team revealed that orexin has a role in learning and expression of stimulus-reward relationships that are important in reward-seeking, drug relapse, and addiction. Using the immediate early gene protein Fos as a marker of neuronal stimulation, the group discovered that Fos-expressing lateral hypothalamus (LH) orexin neurons strongly correlated with preferences for stimuli associated with morphine, cocaine, or a food reward.



*Aston-Jones enjoying some relaxing moments. (Photo courtesy of Gary Aston-Jones)*

Chemical activation of LH orexin neurons reinstated an extinguished conditioned place preference (CPP) for morphine. The Aston-Jones team was able to show that disruption of the projection of orexin neurons to the ventral tegmental area (VTA) prevented learning — a morphine CPP.

Using self-administration methods, his lab also showed that orexin was necessary for stimulus-induced relapse of cocaine-seeking after extinction or abstinence. The team found a similar result for cue-induced reinstatement of extinguished food-seeking. These results led to the conclusion that the orexin system may play an important role in conditioned food craving and obesity.

(Angelika Zaremba, Ph.D., is a visiting postdoctoral fellow in the NIEHS Laboratory of Signal Transduction Inositol Signaling Group.)

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# Extramural papers of the month

By Jerry Phelps

- Cause of vioxx-induced cardiovascular events determined
- GWAS finds asthma gene specific to childhood onset
- Promising target for Parkinson's disease treatment
- Prenatal PAH exposure lowers IQ



Read the current Superfund Research Program [Research Brief](#). New issues are published on the first Wednesday of each month.

## Cause of vioxx-induced cardiovascular events determined

An international research team with funding from NIEHS has discovered a novel mechanism that may explain the heart attacks and strokes suffered by some long-term, high-dosage users of the arthritis drug Vioxx. This groundbreaking discovery may lead to safer drugs for millions of people who suffer chronic pain.

The team employed metabolomic profiling to analyze the plasma of laboratory mice given Vioxx. It found dramatic accumulations of an arachidonic acid metabolite known as 20-HETE. The metabolite is known to be a potent vasoconstrictor, and high levels of it could cause increases in the risk of heart attack and stroke. The research team believes that similar increases might be seen with other non-steroidal anti-inflammatory drugs.

Vioxx was pulled from the marketplace in 2004 after reports of heart attacks and stroke in patients taking the drug. It had been used by millions of people worldwide and showed great promise for disease and conditions marked by chronic pain and inflammation such as arthritis. The UC Davis scientists believe that their findings will open new paths for developing safer COX2 inhibitors. Agents that reduce the circulating levels of 20-HETE while providing the same pain relief may reduce the risk of adverse cardiovascular events.

*Citation:* Liu JY, Li N, Yang J, Li N, Qiu H, Ai D, et al. 2010. Metabolic profiling of murine plasma reveals an unexpected biomarker in rofecoxib-mediated cardiovascular events. *Proc Natl Acad Sci U S A* 107(39):17017-17022.

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## GWAS finds asthma gene specific to childhood onset

A genome-wide association study, funded in-part by NIEHS, identified several gene variants associated with asthma, as well as one that is implicated in childhood asthma. The study was a collaborative effort led by researchers who are members of the GABRIEL consortium — a group of scientists who attempt to identify the genetic and environmental causes of asthma in the European community.

The report notes that the heritability of asthma may be as high as 60 percent. More women than men are affected by adult onset asthma in contrast to childhood asthma, which strikes boys more than girls. Childhood asthma is often linked to allergy, but not in all populations.

The study enrolled more than ten thousand individuals of European descent with asthma and more than sixteen thousand controls. Asthma occurrence before the age of 16 was considered childhood-onset. Almost 600,000 single nucleotide polymorphisms were genotyped in each participant.

The team identified a locus called ORMDL3/GSDMB on chromosome 17 that displayed a significant difference between the strength of its association with childhood asthma and adult onset. Further analysis of this region led the team to conclude that the locus contributes to asthma through the regulation of both genes. The researchers believe that altered expression of ORMDL3 may impair metabolism of sphingolipids, representing a potential mechanism and therapeutic target for the modulation of air inflammation.

*Citation:* [Moffatt MF, Gut IG, Demenais F, Strachan DP, Bouzigon E, Heath S, et al.](#) 2010. A large-scale, consortium-based genomewide association study of asthma. *N Engl J Med* 363(13):1211-1221.

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## Promising target for Parkinson's disease treatment

New research from Johns Hopkins University, with support from NIEHS, demonstrates that certain commercially-available drugs protect nerve cells from the lethal effects of Parkinson's disease in a mouse model. These drugs were shown to be an effective treatment in inhibiting the production of a protein known as LRRK2. This protein is known to be overactive in some Parkinson's patients and causes nerve cells to die.

The researchers monitored LRRK2 autophosphorylation and LRRK2-mediated phosphorylation of myelin basic protein with and without treatment with 70 kinase and phosphorylase inhibitors. Of the 70 tested, eight were found to block the effects of LRRK2 and two of those are known to cross the blood-brain barrier.

These two compounds, known as GW5074 and indirubin-3'-monooxine, were tested in a mouse model of LRRK2 neurotoxicity. Injections of these two drugs twice a day substantially prevented nerve cell death; one was almost completely effective and the other prevented cell loss by about 80 percent. The two drugs have similar structures leading the researchers to envision developing additional compounds around their core structure. The researchers are currently working to design more specific inhibitors of LRRK2 and they plan to license the technology they develop.

*Citation:* [Lee BD, Shin JH, VanKampen J, Petrucelli L, West AB, Ko HS, et al.](#) 2010. Inhibitors of leucine-rich repeat kinase-2 protect against models of Parkinson's disease. *Nat Med* 16(9):998-1000.

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## Prenatal PAH exposure lowers IQ

New findings from a Columbia University study conducted in Krakow, Poland show that prenatal exposure to polycyclic aromatic hydrocarbons reduces IQ in children at five years of age. The study results recapitulate an epidemiologic study done by the same researchers on a population of women and children from New York City.

Healthy, pregnant non-smoking women were recruited into the study from 2001 to 2006. During pregnancy, the women completed a questionnaire and carried a personal air monitor for 48 hours to estimate their babies' exposure to air pollutants. They also provided a blood sample or cord blood sample at delivery. A total of 214 children were followed through 5 years of age. At that time the children were given a standardized intelligence exam called the Raven Coloured Progressive Matrices (RCPM) test.

The median prenatal exposure to PAHs was 17.96 nanograms per cubic meter of air. Children exposed to levels higher than this had an average decrease in IQ by 3.8 points. Adjusting for maternal intelligence, lead exposure or dietary intake of PAH did not alter the results. These findings cause concern because RCPM scores measured during the preschool period correlate with academic achievement later in life. The research team is continuing to follow these children to determine longer-term effects of PAH exposure.

*Citation:* [Edwards SC, Jedrychowski W, Butscher M, Camann D, Kieltyka A, Mroz E, et al. 2010. Prenatal exposure to airborne polycyclic aromatic hydrocarbons and children's intelligence at 5 years of age in a prospective cohort study in Poland. Environ Health Perspect 118\(9\):1326-1331.](#)

(Jerry Phelps is a program analyst in the NIEHS Division of Extramural Research and Training.)

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## Intramural papers of the month

*By Jeffrey Stumpf and Mamta Behl*

- [3D structure of dust mite allergens](#)
- [DNA double-strand breaks may play a role in the mutagenesis of antibody diversification](#)
- [Genome instability due to ribonucleotide incorporation into DNA](#)
- [Effect of alteration in DNA methylation on lymphomas](#)

### 3D structure of dust mite allergens

NIEHS researchers determined the first three-dimensional structure of Der p 5, an allergenic protein produced by a common house dust mite. Immune reactions to Der p 5 and other group 5 allergens are prevalent among allergic patients worldwide. This study revealed that Der p 5 has structural properties that may be important in eliciting allergenic responses.

Der p 5 was shown to be predominantly a monomer, but was also present as a dimer, hexamer, and dodecamer at higher concentrations. The structure illuminated a large hydrophobic pocket at the dimer interface that the authors suggest may be important for binding hydrophobic compounds. The immune system is hypersensitive to hydrophobic molecules from bacteria, which normally stimulate an inflammatory response needed to deter infections. The erroneous stimulation of the immune system by allergens and their hydrophobic "cargo" is believed to skew the immune response toward allergy and away from normal tolerance.

Allergic disease is a major environmental problem that affects one-fifth of the world population. In particular, extrinsic asthma is strongly associated with sensitivity to house dust mites. Illumination of the structure of this allergen furthers the understanding of its role in the origins of allergic disease and may suggest future routes for therapy.

*Citation:* [Mueller GA, Gosavi RA, Krahn JM, Edwards LL, Cuneo MJ, Glesner J, et al. 2010. Der p 5 crystal structure provides insight into the group 5 dust mite allergens. J Biol Chem 285\(33\):25394-25401.](#)

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# DNA double-strand breaks may play a role in the mutagenesis of antibody diversification

Researchers at NIEHS demonstrated a possible role of DNA double-strand breaks (DSBs) in the localized increased mutagenesis necessary for producing different antibodies during the adaptive immune response. This process, called somatic hypermutation, is promoted by activation-induced deaminase (AID), which initiates the mutagenesis process by converting cytosine to uracil in the immunoglobulin genes that encode the regions of antibodies that bind to antigens.

The authors investigated a potential role of DSBs in somatic hypermutation by making use of an earlier report by the Resnick group at NIEHS to engineer yeast strains with two important features: 1) an inducible DSB site positioned downstream of a mutation reporter gene, and 2) inducible expression of recombinant human AID. The authors found that large increases in reporter gene mutagenesis depended on the concurrent induction of a DSB, the expression of AID, and the presence of DNA polymerase delta. These requirements along with the mutation profile in the reporter gene suggested that the mutations were formed by the ability of the DNA polymerase delta to bypass AID-induced uracil bases. Overall, the results are consistent with a model involving single-strand DNA resection at the site of the DSB, and then DNA polymerase delta re-synthesis to fill-in the gap, restoring the double-stranded DNA. Mutations are introduced during the re-synthesis step.

DSBs are prevalent at the immunoglobulin locus and may localize mutagenesis by triggering resection and the formation of regions of single-strand DNA that are substrates for mutation prone re-synthesis of double-stranded DNA. This model may explain how a dangerously mutagenic and carcinogenic process has been modified for a role in maintaining proper immunity.

*Citation:* [Poltoratsky V, Heacock M, Kissling GE, Prasad R, Wilson SH. 2010. Mutagenesis dependent upon the combination of activation-induced deaminase expression and a double-strand break. Mol Immunol September 7 doi:10.1016/j.molimm.2010.08.013 \[Epub ahead of print\]](#)

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## Genome instability due to ribonucleotide incorporation into DNA

DNA is more stable for storing genetic information than is RNA, because the ribose sugar in RNA is intrinsically more prone to strand cleavage that could lead to mutations. Although most DNA polymerases efficiently prevent ribonucleotides from being incorporated into DNA, this exclusion is not absolute. This finding implies that some ribonucleotides will be incorporated into DNA *in vivo*, and that they need to be removed to maintain the chemical identity of organisms like humans, whose genomes are comprised of DNA.

When researchers at the NIEHS and Umeå University in Sweden recently tested these ideas, the results established three important facts about DNA replication:

- Ribonucleotides are indeed incorporated during replication *in vivo*
- The ribonucleotides are normally removed by RNase H2-dependent repair
- Defective repair causes cellular stress and genome instability.

These findings have potentially important implications for human health. Theoretically, the genome instability resulting from loss of ribonucleotide repair could be relevant to humans with inherited defects in RNase H2. These patients suffer from a severe autoimmune disease, Acardi Goutières Syndrome. An RNase H2 defect is also one possible source of genome instability associated with cancer.

Experiments are underway to examine these issues, and to discover the enzymatic mechanisms for the unusual specificity of mutations seen in RNase H2-defective cells. The authors also speculate that the *transient* presence of ribonucleotides in DNA could have beneficial consequences, for example, in signaling for certain important cellular processes.

*Citation:* [Nick McElhinny SA, Kumar D, Clark AB, Watt DL, Watts BE, Lundström EB, et al.](#) 2010. Genome instability due to ribonucleotide incorporation into DNA. *Nat Chem Biol* 6(10):774-781.

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## Effect of alteration in DNA methylation on lymphomas

Recent data suggests that BCL6 oncogene expression is maintained during lymphomagenesis, partly through DNA methylation that prevents CTCF-mediated silencing; CTCF is an enhancer-blocking transcription factor. The research represents a collaborative effort from scientists at NIEHS, Emory University School of Medicine, and SRA International, Inc. It is the first published work to demonstrate the role that DNA methylation plays in the activation of oncogenes.

Abnormal DNA methylation commonly occurs in cancer cells. Although the role of DNA methylation in gene inactivation to promote formation of tumors is well documented, its role in gene activation, particularly of oncogenes had not been clearly demonstrated.

In lymphoma cells, the researchers demonstrated hypermethylation at a specific site on the BCL6 locus that expressed high amounts of BCL6 messenger RNA (mRNA). Consequently, inhibition of DNA methyltransferases decreased BCL6 mRNA abundance, suggesting a role for methylation in the regulation of BCL6 transcription in these cells. In neoplastic plasma cells that do not express BCL6, there was an up-regulation of BCL6 transcription when enhancer-blocking transcription factor CTCF was depleted by short hairpin RNA.

These findings suggest that the fundamental outcome of DNA methyltransferase activity is to alter chemical properties and information content of the DNA subsequently regulating transcription and chromosomal structure.

*Citation:* [Lai AY, Fatemi M, Dhasarathy A, Malone C, Sobol SE, Geigerman C, et al.](#) 2010. DNA methylation prevents CTCF-mediated silencing of the oncogene BCL6 in B cell lymphomas. *J Exp Med* 207(9):1939-1950.

(Jeffrey Stumpf, Ph.D., is a postdoctoral fellow in the NIEHS Laboratory of Molecular Genetics Mitochondrial DNA Replication Group. Mamta Behl, Ph.D., is a research fellow in the NIEHS National Toxicology Program.)

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# Inside the Institute

## Feds aim high to support charities

By Ed Kang

The 2010 Combined Federal Campaign (CFC) at NIEHS has its sights set on a record-setting year. If met, the Institute's goal of \$100,000 would be an all-time high, providing an influx of revenue to non-profits struggling to fund operations in the current economy.



As of mid-October, the halfway point in the campaign, \$62,000 had been pledged versus \$38,000 at the same time last year. "It's a tremendous start," said Linda Birnbaum, Ph.D., NIEHS/NTP director. "Whenever there's a cause to help those in need, federal employees rise to the occasion. Without their support, much-needed programs that provide medical aid to the sick, food to the hungry, and care to the needy might cease to exist."

### A story of success

Chris Long, acting associate director of the NIEHS Office of Management, recalls meeting an inspirational woman named Patti on a recent flight from Washington, D.C. to Raleigh, N.C. "She described how CFC-funded charities had saved her life," said Long.

Four years ago, Patti was unemployed and raising two girls. She took advantage of a free mammogram from one of the non-profit groups and found out she had breast cancer. Another agency helped her figure out how to find and pay for treatment, as well as assistance for taking care of her girls during hospital visits.

Patti is now cancer-free and employed, working in a job that yet another CFC-funded agency helped her find. CFC and the generous donations of employees made it possible.



Michael Watkins loses a staring contest with a visitor from the Carolina Raptor Center. This barred owl was rescued after suffering a broken wing. (Photo courtesy of Steve McCaw)

### Key workers lead the way

Thirty-three dedicated CFC volunteers have been working hard to spread the word to co-workers and help organize several activities designed to boost awareness.

- Sept. 22, a "Meet the CFC Charities" event brought more than 40 local and national non-profits to the Institute.
- Oct. 27, more than 60 runners and walkers came out to support the CFC at the NIEHS/EPA 5K race.
- Nov. 10, NIEHSers will enjoy free ice cream in recognition of their generous support of the campaign.

Also featured this year are raffles of gift certificates to local restaurants and three special baskets filled with gifts donated by CFC volunteers.

“CFC volunteers make it happen,” said Birnbaum. “They’re first in line when the pledging begins, and they continue to give generously of their time throughout the campaign.”

Employees can make pledges to their favorite CFC charities through Nov. 22.

(Ed Kang is a public affairs specialist in the Office of Communications and Public Liaison and a regular contributor to the Environmental Factor.)



*NIEHSers enjoyed sharing their CFC stories with the Ronald McDonald house and other charities that came to visit Sept. 22. (Photo courtesy of Steve McCaw)*



*The Galloping Gene Jockeys of the Division of Intramural Research was one of several teams to participate in the first NIEHS/EPA 5K fundraiser. (Photo courtesy of Ed Kang)*

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## **NIEHS celebrates Hispanic heritage**

*By Melissa Kerr*

In celebration of Hispanic heritage month, the Hispanic Heritage Committee of the Diversity Council invited Ileana Herrell, Ph.D., to NIEHS Oct. 19, to discuss the history and contributions made by persons of Hispanic decent. [Veronica Godfrey](#), chair of the committee, and [Chris Long](#), acting associate director for management at NIEHS, introduced the speaker. Herrell’s talk was titled, “Heritage, Diversity, and Hope: The American Dream.”

### **Celebration of Hispanic culture**

Herrell said that people with familial roots, from the northern border of Mexico to the southern tip of western South America, come from a vast region full of culture. “Several processes were established in Hispanic culture well before they appeared in Europe,” Herrell said. “Some examples include crop rotation and irrigation, a federal government and accounting system among the Incas, the Mayan calendar, and the Mayan zero system, to name a few.”

Although Hispanic culture has played an important role in American culture, Herrell explained that a nationally-recognized time to honor Hispanic contributions didn't happen until 1968 when the U.S. Congress passed, and President Lyndon Johnson signed, a [proclamation](#) designating the week that includes Sept. 15-16 as National Hispanic Heritage week. These two days are when several Latin American countries celebrated their independence, including Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, and Mexico. President Ronald Reagan extended the recognition to cover a month's time in 1988, and today, Hispanic Heritage Month occurs Sept. 15-Oct. 15.

“Several persons of Hispanic decent have become military generals and admirals, scientists, astronauts, Nobel Prize winners, congressmen and congresswomen, senators, and political activists,” Herrell added. “These people have made an indelible mark on United States history.”

When asked why the committee chose Herrell to give the keynote address, Godfrey responded, “[Herrell] represents this community wonderfully. She brings a passion to her job and continues to push for better representation of Hispanic-Americans in the United States on every level.”

### Food and fun with a Latin flavor

Following the presentation, attendees continued the celebration in the NIEHS cafeteria. While the participants enjoyed flan, traditionally prepared pork, and a variety of finger foods, husband and wife pair, Barry and April Dalton, from Barry Dalton School of Dance in Jamestown, N.C., performed several traditional Latin dances. The Daltons were able to talk some of the NIEHS staff members into learning a few steps, as well.

(Melissa Kerr studies chemistry at North Carolina Central University. She is currently an intern in the NIEHS Office of Communications and Public Liaison.)



*Herrell is director of the Division of Scientific Strategic Planning and Policy Analysis at the National Institute on Minority Health and Health Disparities, part of the National Institutes of Health. (Photo courtesy of Steve McCaw)*



*Gerard Roman, right, an NIH Equal Employment Opportunity (EEO) specialist and Dona McNeill of the NIEHS Office of Management, took part in the seminar portion of the Hispanic Heritage activities. (Photo courtesy of Steve McCaw)*



*The Hispanic dishes brought a smile to everyone's face. (Photo courtesy of Steve McCaw)*



*April and Barry Dalton thrill the audience with their Latin dance steps. (Photo courtesy of Steve McCaw)*



*The Hispanic Heritage Committee posed with the speaker, after the seminar. From left to right are Lysandra Castro, Brad Collins, Herrell, Sifre, Godfrey, and Roman. Another member of the committee, Eli Ney, is not pictured. (Photo courtesy of Steve McCaw)*



*Mari Sifre and Benny Encarnacion follow the Dalton's lead and jump into the swing of things. (Photo courtesy of Steve McCaw)*

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