

January 2012

## NIEHS Spotlight



### [Tox21 begins screening 10,000 chemicals](#)

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### [NIEHS collaborates on autism database federation](#)

Funded by NIEHS and four other NIH institutes and centers, the National Database for Autism Research has launched a precedent-setting data-sharing collaboration.



### [Balbus discusses health adaptation at climate change summit](#)

A side event presentation Dec. 8, organized by NIEHS, explored early warning systems and frameworks for vulnerability and adaptation assessments for human health.



### [Copeland named chief of Laboratory of Molecular Genetics](#)

William Copeland, Ph.D., who leads the Laboratory of Molecular Genetics Mitochondrial DNA Replication Group, had served as acting chief since July 2011.



### [Grantee honored by association of science teachers](#)

NIEHS grantee Kathleen Vandiver, Ph.D., was recognized for her more than 20 years of significant contributions to Massachusetts science education.

## Science Notebook



### [2011 papers of the year](#)

Of the nearly 3,000 papers published by NIEHS-supported researchers in 2011, 23 publications were chosen as papers of the year.



### [Distinguished lecturer discusses the mechanism of action of amphetamine](#)

Neuroscientist Susan Amara, Ph.D., gave a presentation Dec. 13 focused on the mechanism of action of amphetamine on dopamine and glutamate transporters.



### [NIEHS selects 2012 ONES awardees](#)

NIEHS has announced funding for seven early stage tenure-track investigators as 2012 Outstanding New Environmental Scientist (ONES) awardees.



### [Researchers find potential new avenue for cancer therapies](#)

The research team, comprised of scientists from NIEHS and several other institutions, published its data online in the Dec. 19 issue of The Journal of Clinical Investigation.



### [Seminar explores the potential of bioinformatics in autism research](#)

Presenters outlined techniques for taking advantage of computational and screening approaches to expand the existing knowledge base surrounding autism.

## NIEHS Spotlight



### [Birnbaum and staff hold conversation with NIEHS Partners](#)

Following morning presentations, Partners enjoyed a nearly three-hour informal lunchtime conversation with NIEHS/NTP Director Linda Birnbaum, Ph.D.



### [Nano Grand Opportunities researchers share findings](#)

This was the final meeting of the consortium, which began in 2009 with 13 two-year grants funded from the American Recovery and Reinvestment Act.



### [mHealth Summit highlights advances in mobile health technology](#)

Representatives from NIEHS joined more than 3,500 leaders from around the world to engage in constructive dialogue about leading-edge mobile health technologies.



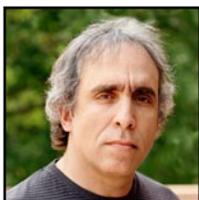
### [NIEHS postdocs learn the value of options at NC biotech career day](#)

NIEHS postdocs joined dozens of their colleagues at the N.C. Biotechnology Center Dec. 9 for the third installment of the organization's Ph.D. career series.



### [Award-winning summer intern accepted by Stanford](#)

NIEHS summer intern Greeshma Somashekar learned in December that one of America's premiere scientific institutions is now officially on her list of possibilities.



### [Freedman represents NIEHS/NTP at conference in Peru](#)

Jonathan Freedman, Ph.D., represented NIEHS/NTP leadership at the II International Congress and IV Peruvian Congress of Toxicology meeting Nov. 21-23 in Lima, Peru.

## Science Notebook



### [Kleckner offers glimpses inside a living \*E. coli\* cell](#)

During a Nov. 21 seminar at NIEHS, Nancy Kleckner, Ph.D., presented exciting findings from her group's recent work on the physical biology of chromosomes.



### [Holian discusses lung inflammation caused by nanoparticles](#)

NIEHS grantee Andrij Holian, Ph.D., presented the latest results from his experiments on the health and safety aspects of engineered nanomaterials Dec. 6 at NIEHS.



### [NTP board moves initiatives forward](#)

Faced with a full agenda of reports and concept clearances, the NTP Board of Scientific Counselors (BSC) accomplished quite a bit during its Dec. 15, 2011, session at NIEHS.



### [Hundreds of rare genetic variants may cause a common autism phenotype](#)

Catalina Betancur, M.D., Ph.D., delivered a presentation Nov. 30 at NIEHS titled "Deconstructing 'idiopathic' autism: One behavioral syndrome, hundreds of genes."



### [NICEATM workshop report on vaccine testing now available](#)

The NTP-sponsored workshop, which is described in the current issue of *Procedia in Vaccinology*, was held Sept. 14-16, 2010, at NIH in Bethesda, Md.

## NIEHS Spotlight



### [NTP advisor named as fellow of the Collegium Ramazzini](#)

NTP Board of Scientific Counselors chair David Eastmond, Ph.D., is among the latest group of fellows selected by the Collegium Ramazzini.



### [Volunteers translate NIEHS cookstove research in Guatemala](#)

NIEHS/NTP Director Linda Birnbaum, Ph.D., received an unexpected holiday gift Dec. 24, thanking her for NIEHS research on respiratory illness and indoor air pollution.

## Inside the Institute



### [Institute staff honored at 2011 NIEHS awards and international day](#)

NIEHS welcomed federal staff and contractors to Rodbell Auditorium Dec. 6 for its annual Awards Ceremony and International Day festivities.



### [CFC enjoys another record year](#)

Combined Federal Campaign Dec. 15, 2011, setting yet another record by raising \$110,000 in pledges from more than 200 employees.



### [NTA celebrates grand opening of resource room](#)

With a ceremonial coffee hour and open house Nov. 30, the NIEHS Trainees Assembly proudly opened the doors to its new resource room in the F module of Building 101.

## Science Notebook



### [Stokes builds international partnerships for advancing alternative testing](#)

Rear Adm. William Stokes, D.V.M., joined other scientists from around the world at meetings in Japan on promoting and validating alternatives to animal testing.



### [Casey presents at international meeting in Hungary](#)

At an expert meeting in Budapest, Nov. 30-Dec. 2, 2011, NICEATM Assistant Director Warren Casey, Ph.D., discussed *in vitro* methods for identifying endocrine disruptors.



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

The journal's lead story for January examines a new strategy for evaluating the impact of regional and local-level climate changes on public health.



### [NIEHS to hold minisymposia on epigenetics and BPA](#)

As part of its Keystone Science Lecture Seminar Series, NIEHS will present minisymposia in January, organized by its Division of Extramural Research and Training.



### [Society for Investigative Dermatology to meet May 9-12 in Raleigh](#)

A diverse group of some 1,500 M.D. and Ph.D. scientists from around the globe will gather to present and exchange findings on dermatology and skin biology.

## Calendar of Upcoming Events

- **Jan. 6**, in Rodbell A, 11:00 a.m.-12:00 p.m. — Laboratory of Reproductive and Developmental Biology Seminar Series featuring Raj Kumar, Ph.D., speaking on “Regulation of Male Germline Stem Cell Niche by FSH”
- **Jan. 10**, in Rodbell Auditorium, 8:30 a.m.-5:00 p.m. — Keystone Science Lecture Seminar Series “Minisymposium: [Epigenetics, Chromatin Biology, Development, and Disease](#),” register
- **Jan. 13 (offsite event)**, in the Levine Science Research Center, Room A247, at Duke University in Durham, N.C., 12:00-1:00 p.m. — Integrated Toxicology and Environmental Health Program presentation by David Armstrong, Ph.D., titled “Endocrine disruption of synaptic plasticity in the postnatal mouse hippocampus”
- **Jan. 16**, in Rodbell Auditorium, 8:00 a.m.-5:00 p.m. — Bisphenol A (BPA) Grantee Meeting
- **Jan. 19**, in Rodbell Auditorium, 1:00-5:00 p.m. — Keystone Science Lecture Seminar Series symposium on BPA
- **Jan. 20**, in Rodbell Auditorium, 8:30 a.m.-5:00 p.m. — Women’s Reproductive Environmental Health Consortium Meeting
- **Jan. 23-24**, in Rodbell Auditorium, 8:30 a.m.-5:00 p.m. — Interagency Breast Cancer and Environmental Research Coordinating Committee Meeting
- **Jan. 30**, in Rodbell B, 11:00 a.m.-12:00 p.m. — Presentation by Michael Diamond, M.D., topic TBA
- View More Events: [NIEHS Public Calendar](#)

## Extramural Research

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

- [Rice consumption and arsenic exposure in pregnant women](#)
- [Consuming canned soup linked to higher BPA levels](#)
- [Dietary compounds could help protect kidney function](#)
- [Estrogen lessens effects of obesity and alcohol on breast cancer](#)

## Intramural Research

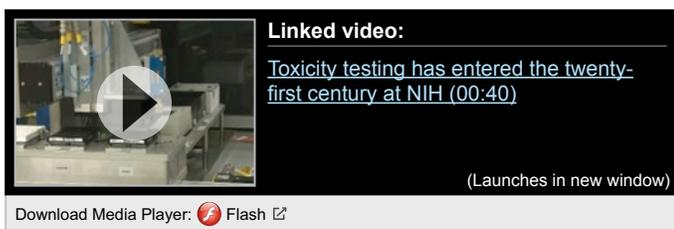
### [Intramural papers of the month](#)

- [Caffeine strengthens connections between neurons in a little-known area of the brain](#)
- [Exposures to certain early-life factors may contribute to an early onset of uterine fibroids](#)
- [Snail and Slug activate TGF-beta in breast cancer](#)
- [Pregnane X receptor regulates liver metabolism](#)

## Tox21 begins screening 10,000 chemicals

By Robin Mackar

In December, a high-speed robotic screening system, aimed at protecting human health by improving how chemicals are tested in the U.S., began testing [10,000 compounds](#) for potential toxicity. The compounds cover a wide variety of classifications, and include consumer products, food additives, chemicals found in industrial processes, and human and veterinary drugs.



Testing this 10,000 compound library begins a new phase of an ongoing collaboration between the National Institutes of Health, the U.S. Environmental Protection Agency, and the U.S. Food and Drug Administration, referred to as [Tox21](#). NIH partners include NIEHS/NTP and the NIH Chemical Genomics Center (NCGC), part of the NIH Center for Translational Therapeutics (NCTT), housed at the National Human Genome Research Institute (NHGRI).

“There has never been a compound library like this before,” said NIEHS/NTP Director Linda Birnbaum, Ph.D.

Birnbaum is especially excited that some of the compounds the NTP has brought forward for testing are mixtures of chemicals. “All of us are exposed to many different chemicals at the same time, not just one chemical at a time,” she said. “These new technologies allow us to more rapidly advance our understanding of not only individual chemicals, but mixtures of chemicals as well.”

A subset of the NTP portion of the 10,000 compound library will focus on pilot testing several formulations or mixtures of compounds, a priority area for NIEHS/NTP. The library constituents were selected after a thorough analysis of existing scientific studies, more than 200 public chemical databases, and chemical nominations received from internal and external partners. Each test compound will undergo a thorough chemical analysis to verify its identity and determine its purity, concentration, and stability.

The goal of the testing is to provide results that will be useful for evaluating whether these chemicals have the potential to disrupt processes in the human body to an extent that leads to adverse health effects.

The compounds will be tested in the Tox21 robotic screening system at the NCGC in Rockville, Md. The Tox21 robot, unveiled earlier this year, was purchased with funds provided by the NTP as part of its contribution to the Tox21 partnership.



*At the dedication of the robotic system in March ([see story](#)), Birnbaum said, “This robot truly exemplifies a remarkable collaboration effort between four federal organizations that showcases how we can all bring our strengths and resources to the table to build the framework for a new predictive toxicology.”*  
*(Photo courtesy of Steve McCaw)*

“The robot has undergone rigorous testing since it was installed and unveiled earlier this year. It’s ready to start testing this large compound library,” said NHGRI Director [Eric Green, M.D., Ph.D.](#) “This is a milestone for Tox21, because it will allow us to test chemicals at a rate previously impossible for anyone to do by hand.”

The development of methods for evaluating chemical toxicity has the potential to revolutionize the assessment of new environmental chemicals and the development of new drugs for therapeutic use.

“We are happy to contribute NCGC’s pharmaceutical collection of approximately 3,500 compounds of approved and investigational drugs as part of the Tox21 program,” said NCTT Scientific Director [Christopher Austin, M.D.](#) “Drug toxicity is one of the primary reasons that the development of new drugs fails and approved drugs are removed from the market, and the ability to better predict toxicity would improve the efficiency of drug development enormously.”

All testing results will be available to the public through NIH and EPA chemical toxicity databases.

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



*Development of high-throughput robotic systems is integral to Green’s vision for NHGRI to integrate genomics and medicine. (Photo courtesy of NHGRI)*

## NIH partners in Tox21

A truly historic collaboration, Tox21 brings together combined resources to help further the individual missions of its members.

The EPA seeks to understand the molecular basis of such chemicals to better protect human health and that of the environment.

“The Tox21 partnership integrates revolutionary advances in molecular biology, chemistry, and computer science, to quickly and cost-effectively screen the thousands of chemicals in use today,” said [Paul Anastas, Ph.D.](#), assistant administrator of the EPA Office of Research and Development. “The innovative robotics screening technology will generate chemical toxicity data that EPA has never had before.”

The FDA, also a partner in Tox21, emphasizes the value of this effort for the public. “The Tox21 rapid assessment of drug toxicity can become a powerful safety tool for protecting the American public. It also has the potential to help bring innovative drugs to market by allowing drug developers to identify unsafe candidate drugs early,” said [Janet Woodcock, M.D.](#), director of the FDA Center for Drug Evaluation and Research.



*Like several other stakeholders in Tox21, Austin hopes that robotic screening can shorten the lengthy 10- to 15-year process of drug development. (Photo courtesy of NHGRI)*

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# NIEHS collaborates on autism database federation

By Eddy Ball

Funded by NIEHS and four other NIH institutes and centers (ICs), the [National Database for Autism Research \(NDAR\)](#) has launched a precedent setting data-sharing collaboration.

NDAR, which is led by the National Institute of Mental Health (NIMH), represents a federation of data with the Autism Genetic Resource Exchange (AGRE), an Autism Speaks program. NDAR may be the largest repository to date of genetic, phenotypic, clinical, and medical imaging data related to research on autism spectrum disorders (ASD), including a portfolio of grants supported by NIEHS for research on environmental factors involved in ASD ([see story](#)).

“Access to this expanded repository of data will be extremely important for NIEHS-funded research,” said Cindy Lawler, Ph.D., the NIEHS health science administrator who oversees the Institute’s autism portfolio. “The ability to ask questions about how genetic and environmental factors act jointly to affect autism risk will be enhanced greatly, as more studies capture data on environmental exposures and share those data through NDAR, where they can be integrated with many other rich data sets that will reside there.” ([See related story](#)).

## Maximizing resources

In a press release Dec. 12, NIMH Director Thomas Insel, M.D., was quoted as saying, “The collaboration between AGRE and NDAR exemplifies the efforts of government and stakeholders to work together for a common cause. NDAR continues to be a leader in the effort to standardize and share ASD data with the research community, and serves as a model to all research communities.”

In the quest to understand ASD and develop preventive and interventional strategies for the disorders, the new federation enables investigators to access data, tools, and computational techniques in NDAR and other major public and private autism databases simultaneously. By integrating results from multiple sources, NDAR provides a rich data set for multiple uses, such as data mining, aggregation, and views into the data supporting research publications.

Databases previously federated with NDAR include Autism Speaks’ Autism Tissue Program, the Kennedy Krieger Institute’s Interactive Autism Network (IAN), and the NIH Pediatric MRI Data Repository. AGRE currently houses a clinical dataset with detailed medical, developmental, morphological, demographic, and behavioral information from people with ASD and their families.



*Lawler oversees some \$7 million of NIEHS funding each year for autism research. (Photo courtesy of Steve McCaw)*



*In a talk at NIEHS earlier this year ([see story](#)), Insel said he welcomed collaborations with environmental health scientists in the search for what factors contribute to ASD. (Photo courtesy of NIMH)*

With the expansion of the NDAR federation to include AGRE, [approved NDAR users](#) will have access to data from the 25,000 research participants represented in NDAR, as well as 2,500 AGRE families and more than 7,500 participants who reported their own information to IAN.

### **A trans-NIH effort**

Along with NIEHS and NIMH, NIH ICs supporting NDAR are the Eunice Kennedy Shriver National Institute of Child Health and Human Development, the National Institute of Neurological Disorders and Stroke, and the NIH Center for Information Technology.

(This story was adapted from an NIMH press release written by Karin Lee. For further information, contact Lee at the NIMH Press Office by phone at 301-443-4526 or by email at [NIMHpress@mail.nih.gov](mailto:NIMHpress@mail.nih.gov).)

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## **Balbus discusses health adaptation at climate change summit**

*By Eddy Ball*

Politicians will no doubt continue to debate in the months ahead about the accomplishments of the latest [U.N. Climate Change Conference](#) held in Durban, South Africa last month ([see text box](#)).

But as delegates struggled with how to stem climate change on the international agreement level, a side event presentation Dec. 8 on “Saving Lives — Advances in Health Adaptation for Climate Change,” organized by NIEHS Senior Advisor for Public Health [John Balbus, M.D.](#), explored early warning systems and frameworks for vulnerability and adaptation assessments for human health. Balbus gave the opening talk describing U.S. efforts to help people and communities become more resilient to the health effects of climate change in their daily lives.

Joining Balbus, who represents the U.S. Department of Health and Human Services (HHS) on the [U.S. Global Change Research Program](#), as speakers at the event were Diarmid Campbell-Lendrum, D.Phil., and Bill Breed. Campbell-Lendrum, a senior scientist in the department of Public Health and Environment at the World Health Organization (WHO), spoke on early warning systems for vector-borne diseases in Africa, and Breed, the director of the Global Climate Change Team at the U.S. Agency for International Development (USAID), described his agency’s activities dealing with famine, drought, and other health issues in Africa.



*Balbus outlined efforts to provide information to the public health community. He said people in every sector need to evaluate the positive and negative effects of adaptation efforts. (Photo courtesy of Steve McCaw)*

### **A year with dramatic evidence of climate change**

Balbus opened his guardedly upbeat talk with a review of the impact of climate change on the people in the U.S. during 2011. He pointed to the record 12 billion-dollar disasters caused by hurricanes, heat waves, drought, wildfire, and floods last year, with near-record levels of summer dryness and rainfall. Equally

disturbing, he added, was a wave of new records for summer nighttime minimum temperatures, interfering with the circadian rhythm that helps people cope physiologically and psychologically with the stress of high daytime temperatures.

The record level of weather stress in 2011, Balbus said, has helped reinforce the message that climate change has serious implications for human health, with some 1,000 deaths directly attributed to events associated with climate change. Across sectors, public health professionals are becoming increasingly interested in preparing for the effects of climate disruption.

### **Integrating research on the health effects of climate change**

“The public health community has really emerged,” Balbus said. “It’s becoming clear to more and more people that many of the measures we need to undertake actually improve health with economic benefits that can offset the cost of climate change mitigation.” The result has been a significant expansion of efforts to better anticipate weather events, identify susceptible populations as far down as to the neighborhood and block level, and integrate awareness of climate change across governmental and professional sectors.

Balbus pointed to support by the Centers for Disease Control and Prevention to state and local public health departments, for needs assessment and mapping studies with GIS software and algorithms to develop effective adaptation programs for early warning and for helping people cope with climate events. He described the upsurge in interagency efforts, such as the interagency crosscutting [Climate Change and Human Health Group](#) co-chaired by NIEHS, and initiatives to bring climate change understanding to bear on the activities of other government agencies to help shape their ongoing activities.

“We have an uphill battle,” Balbus conceded, but increased awareness is helping people learn to ask the right questions about the positive and negative effects of their plans and activities. A new [National Climate Assessment](#), now underway and due for completion in 2013, will improve understanding of climate change impacts across the United States, he added.

Nine new NIH grants administered by NIEHS are supporting research on vulnerability to health effects of climate change, the effectiveness of interventions, and the possible negative effects of some adaptations ([see story](#)).



*“Climate change will generally challenge health systems across the world,” Campbell-Lendrum explained, pointing to the need for what he described as preventive public health plus. His presentation examined parallels between what is being done about adaptation and early warning in the U.S. with what is happening in Africa. (Photo courtesy of WHO)*



*“We’re looking at health in the context of a changing environment,” Breed said. Like his colleagues, he emphasized that climate change research can impact aspects of life in ways that may not be intuitive, such as in agriculture, urban planning, and architecture. (Photo courtesy of the U.S. State Department)*



*In addition to his Dec. 8 presentation, Balbus was also a part of a side event Dec. 7, “U.S. Federal Actions for a Climate Resilient Nation,” which highlighted Executive Branch and private sector actions on climate change. (Photo courtesy of John Balbus)*

## U.N. Climate Change Conference 2011

The 17th Conference of the Parties (COP17) to the United Nations Framework Convention on Climate Change (UNFCCC) and 7th Session of the Conference of the Parties serving as the Meeting of the Parties (CMP7) to the Kyoto Protocol gathered science and policy experts from around the world Nov 28-Dec. 9 for two weeks of discussions and negotiations.

In 1992, Rio de Janeiro hosted the historic Earth Summit, a U.N. event unprecedented both for its size and the scope of its concerns. The 172 states represented there — 108 by heads of state or government — adopted the UNFCCC, which constitutes the political framework to implement and update an international global climate change strategy. The convention allows countries to create instruments to support the mitigation and adaptation efforts of developing countries.

Under the convention, governments gather and share information on greenhouse gas emissions, national policies, and best practices with the goal of launching national strategies for addressing greenhouse gas emissions and adapting to expected impacts, including the provision of financial and technological support to developing countries.

In 1997, the parties adopted an addendum to the convention, known as the Kyoto Protocol, which implements the obligations contained in the convention under the common but differentiated responsibility principle, by establishing specific emission targets for developed countries. Likewise, the protocol establishes the market mechanisms that promote private sector involvement in the global emission reduction effort.

In 2011, for the third consecutive year, the U.S. State Department operated a U.S. Center at the meeting to showcase U.S. climate actions and foster discussion on key issues. The U.S. Center hosted side events at COP17/CMP7 sponsored by U.S. government agencies, such as HHS, and other organizations with interests related to climate change.

# Copeland named chief of Laboratory of Molecular Genetics

By Eddy Ball

NIEHS Scientific Director Darryl Zeldin, M.D., announced Dec. 1 the selection of lead researcher [William Copeland, Ph.D.](#), as chief of the Institute's Laboratory of Molecular Genetics (LMG). Copeland, who leads the LMG's Mitochondrial DNA Replication Group, had served as acting chief since July, when he succeeded longtime LMG Chief Jan Drake, Ph.D.

Congratulating Copeland on his appointment, Zeldin expressed his confidence in Copeland's leadership and his pursuit of scientific excellence. "I have no doubt Dr. Copeland will continue to lead the Laboratory of Molecular Genetics in an outstanding manner, while engaging in cutting-edge research," Zeldin wrote. "Dr. Copeland's research has contributed significantly to the understanding of mitochondrial related diseases, mitochondrial DNA mutagenesis, and the mechanism of toxicity of nucleoside reverse transcriptase inhibitors."

## Mutagenesis central

Considered to be one of the premier centers for the study of environmentally linked genetic mutation, the LMG is composed of nine groups, with some 70 scientists investigating the fundamental mechanisms of genetic stability and instability. Their research into the interplay of environment and mutation has made important contributions to the understanding of a range of human diseases, including cancer, neurological disease, and diseases related to aging.

Copeland, who joined NIEHS in 1993, has devoted his scientific career to the study of what he considers one of the least understood and most intractable to treatment of all human diseases, authoring or co-authoring more than 96 peer-reviewed publications in the field. Among his lab's many breakthroughs in the understanding of mitochondrial disease, the group's studies on changes of mitochondrial DNA replication and stability caused by disease-associated mutations in the sole mitochondrial polymerase have characterized mutations that cause disease, and also described novel methods that allow further characterization of disease mutations and environmental health effects.

"Inherited mitochondrial diseases have a mortality rate roughly that of cancer, with very high rates of premature death," Copeland explains. He is among leading experts who maintain that inherited and induced mitochondrial defects and their effects on energy production also contribute to the common diseases of aging, such as type 2 diabetes, Parkinson's disease, stroke, and Alzheimer's disease.

As head of LMG, Copeland plans to lead by example in the advancement of molecular genetics research. He is also committed to supporting the lab's strong mentoring program. His outstanding contributions to training and career development were recognized by NIEHS trainees with his selection as Mentor of the Year in 2005, and by NIH with the 2006 Director's Mentoring Award.

In addition to his research at NIEHS, Copeland translates his research through service to education and advocacy groups. He is a spokesperson for mitochondrial disease research to researchers, clinicians, and patients through his contributions to the [Mitochondria Research Society](#) as president from 2005 to 2007 and the [United Mitochondrial Disease Foundation \(UMDF\)](#) in several leadership roles ([see text box](#)).



*Copeland chaired the 2011 UMDF symposium in July ([see story](#)), which featured presentations by several NIEHS intramural researchers and grantees. (Photo courtesy of Steve McCaw)*

## Appreciation for service to the United Mitochondrial Disease Foundation

By UMDF CEO and Executive Director Charles Mohan

Dr. Copeland brings fresh insight and energy to the UMDF as he embraces any task we request of him. Along with his past service as the UMDF Grant Review Committee co-chairman and chairman from 2004 to 2008, he continues to review UMDF grant applications. As chair of the UMDF Research Policy Review Committee, Dr. Copeland leads the review of UMDF-funded grant project reports and makes recommendations regarding new precedent-setting grant policies. He is on the UMDF Ask the Mito Doc team, answering basic research and genetics questions for our patients and family members. Dr. Copeland serves on the Scientific and Medical Advisory Board and the 2012 symposium planning committee. He was chair of the 2011 symposium planning committee and served on the committee for four years prior to that, as well.

Dr. Copeland is a real teacher, and is looked up to as a leader in the mitochondrial community, both lay and professional. Molding the minds of future generations of researchers, he encourages his entire lab staff to attend our symposium, gives leading-edge symposium lectures, and participates in informal conversations with lay and scientific attendees.

To say that we at the UMDF appreciate and enjoy Dr. Copeland is an understatement. Having him on our team has directly enhanced our mission to promote research and education for the diagnosis, treatment, and cure of mitochondrial disorders, and to provide support to affected individuals and families.

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## Grantee honored by association of science teachers

NIEHS grantee Kathleen Vandiver, Ph.D., became a member of the [Massachusetts Hall of Fame for Science Educators](#) during the annual conference of the [Massachusetts Association of Science Teachers](#) in November 2011. The award honors Vandiver's more than 20 years of significant contributions to Massachusetts science education.

Vandiver is co-director of [community outreach and education core](#) for the NIEHS-funded Massachusetts Institute of Technology (MIT) [Massachusetts Center for Environmental Health Sciences \(CEHS\)](#). Vandiver's programs help to create engaging ways to teach abstract scientific concepts, such as molecular genetics, with models made from LEGO bricks.

“Kathy has done an excellent job of using the LEGO kit to help students and teachers understand the links between environmental exposures and human health,” said NIEHS Program Analyst Liam O’Fallon. “It is a truly engaging approach that makes CEHS education and outreach more effective.”

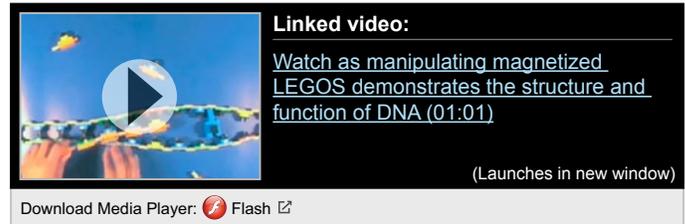


*Shown, left to right, Thomas Vaughn, head and chair of Massachusetts Hall of Fame for Science Educators, joined Vandiver and Richardson at the presentation. (Photo courtesy of Kim Vandiver)*

## Appealing to the senses to communicate abstract concepts

“It isn’t just that I make models,” said Vandiver, who taught sixth-grade science in Lexington, Mass., from 1990 to 2005. “What’s different is I design the projects so that the models and lessons intrinsically emphasize the key concepts instead of all the details. And it’s helpful for students to engage with the point of the lesson in a tactile, memorable way.”

Vandiver continues to explore how to make abstract concepts clear to students. A recent exhibit in the MIT Museum, Learning Lab: The Cell, used LEGO bricks put together by the participants to emphasize the connection between DNA and health.



In an MIT Edgerton Center project, funded in part by the National Aeronautics and Space Administration (NASA) and supported by CEHS, Vandiver is currently collaborating with the Boston public schools system’s science department to pilot the hands-on LEGO DNA curriculum in biology classes, and to provide teacher professional development sessions and classroom support. The project, which began in May 2010, was implemented last spring and continues this year. The materials are very popular with teachers and students, especially English as a Second Language students.

Marilyn Richardson, a teacher who nominated Vandiver, first met her at an MIT CEHS teacher summer workshop in 2007. Richardson said, “I hadn’t taught life science in many years, and working with the LEGO kits helped me refocus on biological issues and helped me do a better job of teaching.” Sixth-graders and AP biology students alike are picking up the concepts, as well as adult learners such as nurses and engineers, corroborating that the models embody universal design principles. Different LEGO sets have been created to address the fundamentals in DNA, proteins, protein synthesis, cell division and chromosomes, and chemical reactions such as photosynthesis.

Vandiver said she was pleased to be recognized for creating tools for hands-on learning, and noted there are many worthy and deserving teachers in Massachusetts, whose work CEHS appreciates and wishes to honor.

(This story was adapted from a Dec. 8 MIT news [release](#) by Debbie Levey, an editor at the MIT Department of Civil and Environmental Engineering.)

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## Birnbaum and staff hold conversation with NIEHS Partners

*By Eddy Ball*

The NIEHS Public Interest Partners joined in a conversation with NIEHS/NTP Director Linda Birnbaum, Ph.D., and staff Dec. 1 in Friendship Heights, Md. While the meeting featured engaging presentations on nanomaterials research by key NIEHS/NTP scientists, the gathering also offered Partners an opportunity to shape the afternoon agenda during an almost three-hour informal lunchtime conversation on a variety of topics.

The NIEHS director and staff meet periodically with the [Public Interest Partners](#) to seek input and improve communication with communities and organizations directly affected by the mission and research of NIEHS. The membership represents diverse groups including disease, disability, and environmental education and advocacy organizations. The group lends grassroots perspectives to the research agenda of NIEHS, and serves as a key contributor to the translation of research findings for the public, policy makers, and private foundations.

During her introductory comments, Partners co-chair Karen Miller, who is president of the Huntington Breast Cancer Action Coalition, described the productive long-term relationship between NIEHS and the Public Interest Partners. “Over the years the Partners have had many opportunities to contribute and participate,” she said. The support provided by NIEHS to share information among NGOs [non-governmental organizations] is invaluable.”

### A primer on nanomaterials

The rapidly growing number of products that contain nanomaterials entering the market each year poses a concern for environmental health scientists because so little is known about the possible harmful health effects of exposure.

Although the nanomaterials are manufactured from well-studied elements, such as carbon, nickel, and gold, manipulation of size, shape, and other physical and electrical properties can make them behave much differently than their parent elements. At the nano level, materials can also become more bioactive because they can pass through membrane barriers in the body more easily than micro-scale or larger particles. Understanding nanomaterials is made even more challenging because different manufacturing processes can mean the same product, such as a single-wall carbon nanotube, may behave differently depending on where it was produced.

To offer their insight on nanomaterials and nanotechnology, scientists representing the three divisions at NIEHS presented reports on their research agendas:

- Division of the NTP Deputy Director for Science [Nigel Walker, Ph.D.](#), spoke on hazard assessment
- Division of Extramural Research and Training Scientist Health Administrator [Sri Nadadur, Ph.D.](#), described the NIEHS nanomaterials grant portfolio
- Division of Intramural Research respiratory biology lead researcher and Clinical Research Unit Medical Director [Stavros Garantziotis, M.D.](#), discussed basic research at NIEHS



*During lunch and into the mid-afternoon, Birnbaum, center, let the Partners direct the conversation. (Photo courtesy of John Schelp)*



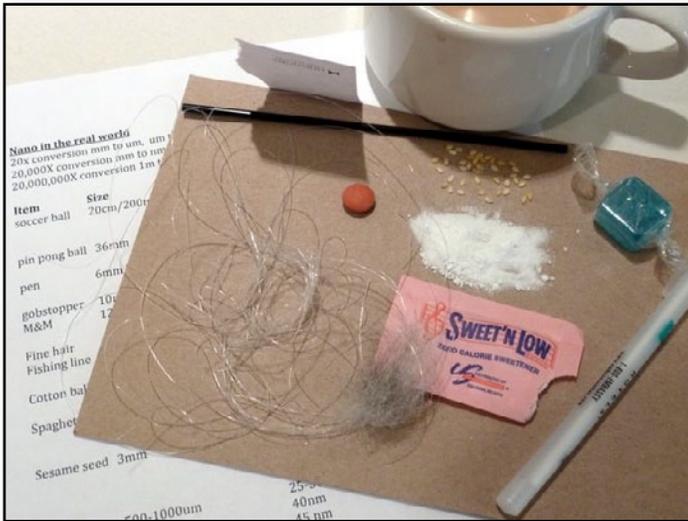
*Leyla McCurdy, senior director at the National Environmental Education Foundation, expressed her appreciation for the Partners meetings. “NIEHS has contributed tremendously to the scientific knowledge on environmental health and has made it easily accessible to us, empowering us to educate our constituents.” (Photo courtesy of John Schelp)*



*Garantziotis, above, and his fellow scientists spoke from their seats, reinforcing the conversational informality of the gathering. (Photo courtesy of John Schelp)*

“The presenters at the Partners meeting took the mystery out of nanotechnology,” Betty Mekdeci, executive director of Birth Defect Research for Children and Partners co-chair, said afterwards. “We were introduced to the subject though a fascinating show and tell presentation followed by the basic science and possible adverse effects of nanotechnology.”

Mekdeci and colleagues also appreciated the open-ended lunchtime discussion. “The afternoon was a lively and energetic Q and A [question and answer] exchange between Dr. Birnbaum and all the Partners,” she said.



Walker left behind the staples of scientific lectures, the podium and PowerPoint slides, but he brought along familiar items to demonstrate the different sizes and shapes of nanomaterials. (Photo courtesy of John Schelp)

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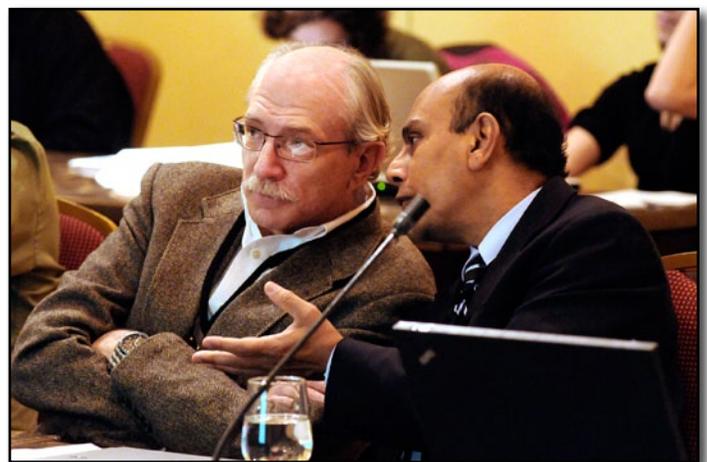
The seating arrangement helped NIEHS representatives interact with individual Partners. Shown, left to right, NIEHS Toxicology Liaison Chris Weis, Ph.D., joined Partners members Kari Christianson, program director with DES Action USA, and Virginia Ladd, president and executive director of the American Autoimmune Related Diseases Association. (Photo courtesy of John Schelp)

## Nano Grand Opportunities researchers share findings

By Thaddeus Schug

Members of the NIEHS nanotechnology Grand Opportunities (Nano GO) grant program gathered Dec. 8-9, 2011, in Research Triangle Park, N.C., to update their research efforts on engineered nanomaterials (ENMs). This was the final meeting of the consortium, which began in 2009 with 13 two-year grants funded from the American Recovery and Reinvestment Act. The primary goals of this program were to develop reliable and reproducible methods and models to assess exposure, exposure metrics, and biological response to nanomaterials.

The 13 grantees were brought together into a consortium to facilitate interdisciplinary communication, develop research synergies, and conduct collaborative research



Nadadur, right, chatted with NIEHS Deputy Director Rick Woychik, Ph.D., during the meeting. Woychik has taken special interest in the nanotechnology programs at NIEHS. (Photo courtesy of Steve McCaw)

projects. Several other NIEHS-funded researchers, with interests in nanotechnology, also joined the consortium and provided valuable experimental input. The Nano GO consortium functions as a framework for grantees to work together toward the common goal of developing methods to achieve greater harmonization of research results for hazard assessment of ENMs.

Sri Nadadur, Ph.D., the meeting organizer and a health scientist administrator at NIEHS who oversees much of the Institute's portfolio on nanomaterials in health and safety, explained, "We have seen a great deal of progress in meeting the overall goals of the consortium. This group of scientists worked through many challenging technical issues that are unique to nanomaterials, to develop protocols and achieve reliable and reproducible experimental results."



*James Bonner, Ph.D., an associate professor in the Department of Environmental and Molecular Toxicology at North Carolina State University, was a leader in developing protocols for the in vivo testing experiments. (Photo courtesy of Steve McCaw)*

### **Consortium activities**

The Nano GO consortium was an active hub of communication among grantees for the duration of the two-year funding period between 2009 and 2011. The consortium provided frequent opportunities for researchers to interact, as they worked closely together to plan, implement, and troubleshoot both individual and collaborative research projects.

A kickoff meeting in 2009 introduced researchers to the diverse skills and areas of expertise represented by the consortium members, and allowed them to begin planning collaborative projects. Progress meetings in 2010 and 2011 enabled participants to assess preliminary results, and refine their methods to address challenges and inconsistencies.

During this meeting, consortium members shared final results and summarized lessons learned. In between these four in-person meetings, consortium members communicated through frequent conference calls, to share experiences and results, identify problems, and refine methods and protocols.



*Andre Nel, M.D., Ph.D., a professor and division chief of NanoMedicine at the University of California, Los Angeles, and his lab contributed to both the in vitro and in vivo round-robin experiments. (Photo courtesy of Steve McCaw)*

### **Round-robin test results**

In addition to individual projects, consortium researchers conducted several collaborative research projects. These were structured as a series of round-robin tests, in which similar or identical methods were used to perform in vitro and in vivo tests concurrently at thirteen different laboratories around the country. Researchers worked together to design the overall structure of the tests, identify target ENMs, determine appropriate assays, select cell and animal models, and refine research methods and protocols as the tests proceeded ([see text box](#)).

The researchers plan to publish the results from these studies in two separate papers, later this year, in the NIEHS publication *Environmental Health Perspectives*.

## Round-robin testing of ENMs

The consortium chose several well-studied and commercially abundant nanomaterials that also possessed a wide range of physical and chemical properties, including zinc oxide (ZnO); three forms of titanium dioxide (TiO<sub>2</sub> P25 sphere, anatase, or angular, sphere, and anatase nanobelt); and three multi-walled carbon nanotubes. The selected ENMs were characterized centrally, to ensure consistency of test materials across all laboratories and provide a shared source of detailed, accurate information about the materials.

*In vitro* studies were performed at eight laboratories. Two cell viability assays (MTS and LDH) and a pro-inflammation cytokine assay (IL-1b) were used to assess the effects of 24-hour exposure to ZnO, TiO<sub>2</sub>, and carbon nanotubes on three cell lines.

*In vivo* studies were performed at seven laboratories, with four using mice and three using rats. Mice were exposed to TiO<sub>2</sub> nanomaterials and carbon nanotubes through oropharyngeal, or mid-throat, aspiration. Rats were exposed to TiO<sub>2</sub> nanomaterials through intratracheal instillation, administering the ENM in vehicle directly to the lung and bypassing the nasal cavity.

Effects were measured at various time points using total cell numbers, differential cell counting to show effects on neutrophilia, imaging of ENMs in bronchoalveolar lavage cells, histopathology images, total protein levels, and levels of lactate dehydrogenase (LDH), a marker for acute or chronic tissue damage.



Shown, left to right, consortium members Frank Witzmann, Ph.D., Edward Crandall, M.D., Ph.D., and Galya Orr, Ph.D., participated in meeting discussions. (Photo courtesy of Steve McCaw)



Kent Pinkerton, Ph.D., left, led a group of researchers studying the pulmonary effects of ENMs in rats. Nigel Walker, Ph.D., right, is the NTP lead on the nanotechnology safety program. (Photo courtesy of Steve McCaw)

(Thaddeus Schug, Ph.D., is a health scientist administrator in the NIEHS Division of Extramural Research and Training (DERT) and a regular contributor to the Environmental Factor. Prior to joining DERT in 2011, he was a postdoctoral research fellow in the NIEHS Laboratory of Signal Transduction.)

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# mHealth Summit highlights advances in mobile health technology

By Ryan Campbell

Representatives from NIEHS and the National Clearinghouse for Worker Safety and Health Training joined more than 3,500 leaders from technology, business, research, and policy communities around the world to engage in constructive dialogue about the role of mobile health technologies in the 21st Century, at the 2011 [mHealth Summit](#) Dec. 5-7, 2011, in Washington, D.C.



**What is mHealth?**



**Linked video:**  
Watch a full-screen expandable video on mHealth (02:43)

(Launches in new window)

Download Media Player:  Flash 

Representing NIEHS at the meeting were staff from the [Worker Education and Training Program \(WETP\)](#) and the Division of Extramural Research and Training.

Smart phones with internet capabilities have changed the way in which people manage their health. mHealth delivers on-the-go health information to smart phones via applications and Internet-based Web pages. mHealth can teach someone how to eat a healthy diet, manage diabetes, choose a doctor, or quit smoking. In 2011, smart phones accounted for more than half of cell phone sales, so the possibility of disseminating health information and managing an individual's health has limitless potential.

This year's summit featured keynote speakers Kathleen Sebelius, secretary of the U.S. Department of Health and Human Services, and Regina Benjamin, M.D., the U.S. surgeon general. "When we talk about mobile health, we are talking about taking the biggest technology breakthrough of our time and using it to take on one of the greatest national challenges of our time," Sebelius said in her keynote address. The three-day event included fourteen concurrent themed track sessions covering a wide range of mobile health topics related to business, policy, research, and technology.

## The NIEHS presence at mHealth

David Balshaw, Ph.D., NIEHS program administrator for the [NIH Genes, Environment, and Health Initiative Exposure Biology Program \(EBP\)](#), led a session and presented research about recent technological advancements related to monitoring environmental exposures that interact with a genetic variation to result in human disease. The presentation included demonstrations of monitoring devices to aid in minimizing human exposure to health-impairing pollutants.



*Hughes, left, and Bandera talked in front of the WETP poster about Cell Podium's services for just-in-time training for emergency incidents. Information messages and videos can be broadcast to individuals who need information, just at the time they need it, to respond to an emergency or learn about their health. (Photo courtesy of Chip Hughes)*

“The term mHealth may be vague but there is no refuting the tremendous progress being made along technological fronts,” explained Cesar Bandera, Ph.D., a WETP grantee and developer of the Cell Podium mobile multimedia messaging service, who presented a poster in conjunction with the National Library of Medicine and NIEHS. “The Summit also conveyed an increased focus on system integration, such that mobile devices operate within a process involving the patient, care provider, and payer.” Bandera presented his research, illustrating the functions and utilization of mobile technology, during the poster session at the summit.

The National Clearinghouse for Worker Safety and Health Training had an opportunity to network and provide information and outreach at the NIEHS information booth in the mHealth exhibitor’s hall. Clearinghouse staff also answered summit attendee questions about NIEHS, its programs, and its development of mobile health technologies.

(Ryan Campbell is on the staff of MDB, a contractor for the WETP and NIEHS Superfund Research Program.)



*Balshaw oversees EBP grants that, among other things, are dramatically improving the quality and reducing the size of personal monitoring devices that can warn of exposures to hazardous agents and communicate real-time information about exposure to researchers. (Photo courtesy of Steve McCaw)*

## Funding opportunity

A recent [Funding Opportunity Announcement \(FOA\)](#) issued Dec. 5, 2011, solicits Small Business Innovation Research (SBIR) for novel technologies that are field-deployable and lab-based, highlighting the NIEHS commitment to mHealth.

“There is an urgent need for mobile technology development, to identify exposures within communities and to relay health and safety information in a timely manner,” said Chip Hughes, director of the NIEHS Worker Education and Training Program.

Grantees, such as Bandera, have demonstrated the potential of multimedia messaging in patient education. Through a [grant](#) from NIEHS, and in conjunction with the NIEHS Center for Environmental Exposures and Disease at the University of Medicine and Dentistry of New Jersey, Cell Podium broadcasts [videos](#) on breast cancer and the environment, on a weekly basis to cell phone users who sign up for a subscription via email at [breastcancer@cellpodium.com](mailto:breastcancer@cellpodium.com).



*MDB employees Ryan Campbell, left, and Dusty Russell, worked the NIEHS display in the NIH Pavilion at the mHealth Summit. (Photo courtesy of Chip Hughes)*

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# NIEHS postdocs learn the value of options at NC biotech career day

By Ian Thomas

NIEHS postdocs joined dozens of their colleagues at the [North Carolina Biotechnology Center \(NCBC\)](#) Dec. 9 for the third installment of the organization's career series, titled "Science Industry Careers: Discovery to Product Development." Held at NCBC's main facility in Research Triangle Park, the event exposed attendees to a range of industry career paths, available to scientists who hold a Ph.D.

"Science and pharmacology are no different than any other field when it comes to the job market," said [Drew Applefield, Ph.D.](#), a business and technology development associate with NCBC and the event's moderator. "With that in mind, we wanted to give new scientists entering these fields a chance to explore their options, both in and out of research, as well as a chance to network with actual members of the industry."

Spanning the majority of the day, the event consisted of three primary segments. The first featured a discussion of the drug development process, while the second addressed the role of regulatory affairs. Finally, the day concluded with a panel discussion and a resume review session.

According to several attendees, the workshop added to their understanding of career options. "I learned a lot today, particularly with regard to the drug development process and the regulations that deal with it," said NIEHS trainee Emily Zhou, Ph.D.

## A complex process

Led off by Jonathan Stocker, the associate director of clinical development for ClinPharm Consulting, the morning began with a step-by-step breakdown of the New Drug Application (NDA) development process. Stocker discussed the pre-clinical, or discovery stage, the clinical stage, featuring the three phases of clinical trials, the FDA evaluation stage, and finally the post-approval, or commercialization stage.

"Moving an NDA from the bench top, through lead optimization into the clinical stage alone is a long and complicated process that takes many years," said Stocker, who focused much of his presentation on the pre-clinical and clinical stages. "Making this process happen requires a wide range of people from both the academic and entrepreneurial arenas. So it really behooves new scientists to become familiar with both."



Stocker said of the long and expensive process of drug development, "It's hard, but very exciting." (Photo courtesy of Steve McCaw)



NIEHS postdoctoral fellow Emily Zhou, Ph.D., took advantage of the morning break to network with Schuller and learn more about careers in regulatory affairs. (Photo courtesy of Steve McCaw)

## Regulating an industry

In the second session, attendees were versed in the world of pharmaceutical regulatory affairs. As described by Charity-Anne Schuller, Ph.D., associate director of regulatory affairs for PPD Inc., this field involves reading, understanding, and interpreting of laws surrounding drug development, so as to insure proper compliance on the part of manufacturers.

“Ultimately, the role of the FDA is to protect the public health by passing laws that assure the safety, efficacy, and security of the medical products on the market,” said Schuller, an adjunct professor with Campbell University’s clinical research program. “That requires a fluent understanding of a lot of complex topics which means that we, as regulatory specialists, can often times find ourselves wearing a lot of different hats within the companies we work for.”

## Shifting gears

The NC Biotech career day concluded with a panel of four members, each of whom began their careers as research scientists before eventually moving into industry. Throughout the hour, panelists took turns answering questions from the audience, while sharing their respective experiences and insights about the field. While their stories may have differed, their advice to attendees was unanimous.

“Always know your options,” said Amber Barnes, Ph.D., a panelist and senior medical writer who began her career as an oncology researcher. “Not everyone is cut out to spend their entire career working from the bench, and if you decide to shift gears, like I did, it’s up to you to arm yourself with the tools you’ll need to make that transition.”

The Ph.D. career workshop series was organized by Shobha Parthasarathi, Ph.D., technology development director of the BCNC Business and Technology Development Program and head of the Center’s Industrial Fellowship Program (IFP). The first two sessions focused on “Life Science Industry Careers: Bench to Boardroom” and “Agencies and Research Institutes.”

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

## Career Day Panelists

- Amber Barnes, Ph.D.
  - Senior Medical Writer, Pharmanet/i3
- Bob Black, Ph.D.
  - Vice President, Scion NeuroStim
- Dominique Pifat, Ph.D.
  - Senior Consultant, Biologics Consulting Group
- Leo DiNapoli, Ph.D.
  - Associate Director for Regulatory Affairs, Cato Research



Meanwhile, NIEHS postdoc Andy Seipel, Ph.D., used his break to talk with colleagues from other institutions. According to Parthasarathi, the workshop attracted Ph.D.s from as far away as East Carolina University. (Photo courtesy of Steve McCaw)



The panelists talked about their circuitous career paths and how they’ve become comfortable with change. Shown above are Pifat, right, and DiNapoli. (Photo courtesy of Steve McCaw)



*Black, an engineer who now works in medical device development for a small firm, has also worked in academia and for a large corporation. He described his career as a random walk. (Photo courtesy of Steve McCaw)*



*Barnes, who seems to flourish in the shifting environment of the private sector, told the audience, “Don’t feel that you’re making a decision for the rest of your life.” (Photo courtesy of Steve McCaw)*

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## Award-winning summer intern accepted by Stanford

*By Ian Thomas*

After spending much of her fall semester applying to colleges, NIEHS summer intern Greeshma Somashekar learned in December 2011 that one of America’s premiere scientific institutions is now officially on her list of possibilities. An award-winning member of the 2011 NIH [Summer Internship Program at NIEHS](#), Somashekar was formally accepted into prestigious Stanford University as part of the class of 2015.

“I was ecstatic to get the news,” recalled Somashekar, a senior at the [North Carolina School of Science and Mathematics \(NCSSM\)](#) in Durham, N.C. “Stanford has excellent schools in engineering and the sciences, and the idea of studying in such a collaborative learning environment, with that many resources, is really remarkable to think about.”

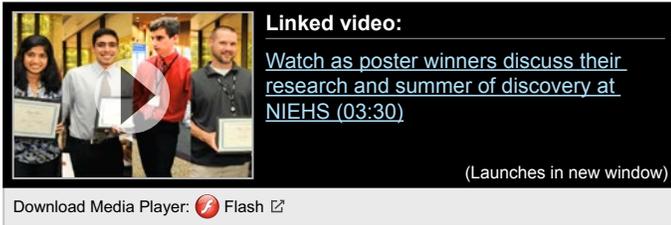
While at NIEHS, Somashekar spent the bulk of her time in the Institute’s Matrix Biology Group. Working under the watchful eye of [Stavros Garantziotis, M.D.](#), medical director of the NIEHS Clinical Research Unit, she quickly established herself as a part of the group, researching proteins in lung tissue.

“Stanford has made a tremendous selection,” said Garantziotis. “Greeshma was an outstanding student in her time with us, and both the university and the scientific community, as a whole, would be fortunate to have her.”



*During the Summer Internship Program poster session July 28, 2011, Somashekar, right, was on hand at her poster to explain her findings and methodology to fellow interns, postdoctoral fellows, and senior scientists. (Photo courtesy of Steve McCaw)*

In addition to capturing top high school student honors for her [poster presentation](#) at the conclusion of the summer, Somashekar was also featured in an NIEHS video chronicling the students' time in the Summer Internship Program.



### A journey of great expectations

Before her possible move to the West Coast, Somashekar has a busy schedule to complete in 2012 at NCSSM. As one of four finalists in the [North Carolina International Science Challenge](#), she and her peers will travel to China in March to represent the U.S. at the Beijing Youth Science Creation Competition.

“Having your research recognized by a panel of your peers is always a great feeling, but having the opportunity to present that work on the international stage is truly an incredible honor,” she said, noting her excitement about getting to see the Great Wall of China.

### A true love of science

Still, as happy as she is about her accomplishments and the chance to travel abroad, Somashekar is the first to point out that it always has been, and will continue to be, about the science.

“Naturally, I’m sure my research interests will evolve over time, but for now I find myself really drawn to biomedical engineering,” she said, adding that she hopes to earn her undergraduate degree in either bioengineering, biomedical computation, or human biology, before eventually attending medical school. “In many ways, we’re only now scratching the surface of how computer science can influence medical research, and that’s really exciting stuff to me.”

(Ian Thomas is a public affairs specialist for the NIEHS Office of Communications and Public Liaison and a regular contributor to the Environmental Factor.)

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## Freedman represents NIEHS/NTP at conference in Peru

*By Eddy Ball*

Try as she may, NIEHS/NTP Director Linda Birnbaum, Ph.D., can’t attend every major meeting that NIEHS co-sponsors. For one such meeting, the II International Congress and IV Peruvian Congress of Toxicology in Lima, Peru Nov. 21-23, 2011, Birnbaum tapped NIEHS/NTP lead researcher [Jonathan Freedman, Ph.D.](#), to attend in her place.



*Garantziotis also serves as the principal investigator for the NIEHS Laboratory of Respiratory Biology. (Photo courtesy of Steve McCaw)*

Freedman is head of the NTP Biomolecular Screening Branch WormTox Group, which uses medium-throughput screening to study response to transition metals in a nematode, or roundworm, model. “Linda felt the content of the meeting would be interesting to the NIEHS community,” Freedman said afterwards. “Also, she likes the idea of Institute scientists going to less frequented locations to promote the NIEHS mission and environmental health in general.”

### Advancing global environmental health

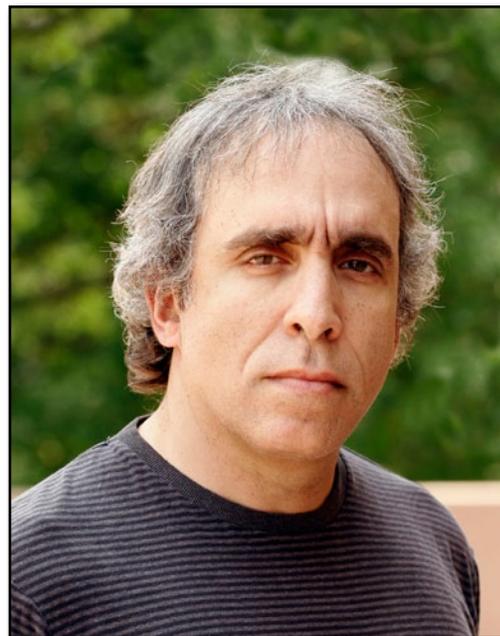
“NIEHS can contribute a lot to emerging cross-disciplinary toxicology programs worldwide,” Birnbaum explained. “Not surprisingly, toxicologists in developing countries look to NIEHS/NTP as a model for what good programs should be doing.”

The congress was organized by the Academic/Professional School of Toxicology of the National University of San Marcos in Lima, the oldest university in South America and widely considered the leading university in Peru. Like many developing countries, especially ones with a wealth of mineral resources, Peru is faced with developing the scientific infrastructure to deal with threats to its population’s environmental health.

The goals of the congress were to promote a multidisciplinary approach to general and environmental toxicology, disseminate information about risks to health and the environment from toxicants, stimulate scientific investigation especially in the area of mechanisms of toxicity, and emphasize the need to prevent, detect, and treat intoxications. The agenda included a series of pregress courses, roundtables, themed conferences, and platform sessions.

The Spanish Society of Toxicology co-sponsored the event. Society of Toxicology (SOT) member participation in the congress and other scientific activities in Peru was funded by the SOT Education Committee through the Global Toxicology Scholar Program.

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*NIEHS/NTP representative Jonathan Freedman (Photo courtesy of Steve McCaw)*



*Crest of the National University of San Marcos*

## NTP advisor named as fellow of the Collegium Ramazzini

*By Eddy Ball*

NTP Board of Scientific Counselors chair [David Eastmond, Ph.D.](#), is among the latest group of fellows selected by the Collegium Ramazzini, an organization of international scholars who work towards solutions of occupational and environmental health problems around the world.

Eastmond is a professor of cell biology at the University of California, Riverside (UCR) and chair of the university’s Department of Cell Biology and Neuroscience. He is actively involved in research and teaching in the areas of toxicology and risk assessment. Along with his service on the NTP Board of Scientific Counselors, Eastmond has contributed to a number of U.S. and international panels on genotoxicity and carcinogens.

In a UCR [press release](#) issued Nov. 28, 2011, Eastmond was quoted as saying, “I am very pleased and honored to be selected as a fellow of the Collegium Ramazzini, and look forward to working with this esteemed group.”

### **Recognition for international distinction in environmental health**

With [190 fellows](#) from countries around the world, the [Collegium Ramazzini](#) is an international scientific society that examines critical issues in occupational and environmental health, with a view towards action to prevent disease and promote health. The fellows are professionals of clear personal distinction and integrity, distinguished by their contributions to occupational and environmental health.

Eastmond joins the select group of Collegium Ramazzini fellows, which includes several current and former NIEHS scientists, advisors, and grantees. NIEHS/NTP Director Linda Birnbaum, Ph.D., former NIEHS Director Kenneth Olden, Ph.D., NTP Associate Director John Bucher, Ph.D., and Superfund Research Program Director William Suk, Ph.D., are fellows, along with other outstanding past and present NIEHS scientists, including Carl Barrett, Ph.D., David Hoel, Ph.D., James Huff, Ph.D., George Lucier, Ph.D., Ronald Melnick, Ph.D., and Walter Rogan, M.D.

Former NIEHS Director David Rall, M.D., Ph.D., was the recipient of the annual [Ramazzini Award](#) in 1989. One of Eastmond’s colleagues on the NTP Board of Scientific Counselors, Melissa McDiarmid, M.D., of the University of Maryland, is also a Collegium Ramazzini fellow.

### **The Collegium Ramazzini carries on the legacy of the father of occupational medicine**

Founded in 1982, the Collegium derives its name from Italian physician and University of Modena Professor Bernardino Ramazzini (1633–1714), who authored one of the founding and seminal works of occupational medicine and played a substantial role in its development. His book, *De Morbis Artificum Diatriba* (Diseases of Workers), outlined the health hazards of chemicals, dust, metals, repetitive or violent motions, odd postures, and other disease-causative agents encountered by workers in 52 occupations.

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*Collegium Ramazzini fellow David Eastmond  
(Photo courtesy of UCR)*



DA VENIAM SCRIPTIS QUORUM NON GLORIA NOBIS  
CAUSA, SED UTILITAS OFFICIUMQUE FUIT

*The collegium’s logo features an 18th century drawing of the group’s namesake, Bernardino Ramazzini. (Photo courtesy of the Collegium Ramazzini)*

# Volunteers translate NIEHS cookstove research in Guatemala

By Eddy Ball

NIEHS/NTP Director Linda Birnbaum, Ph.D., received an unexpected holiday gift Dec. 24, thanking her for NIEHS research on respiratory illness and indoor air pollution.

The note, from biochemist John Paulsrud, Ph.D., a member of the Zionsville [Ind.] United Methodist Church and a retired research staff member at Indiana University School of Medicine, pointed to a recent report about research led by NIEHS grantee Kirk Smith, Ph.D. Smith estimates that indoor air pollution from cooking over open fires kills almost 1.6 million children worldwide each year ([see story](#)).

The United Press International online [report](#), Paulsrud said, helped raise his congregation's awareness of the potential preventive health impact of efficient wood-burning cookstoves for people in developing countries, inspiring one member to donate funds to purchase 100 Guatemalan-produced stoves for indigenous Mayans.

"To date," Paulsrud wrote, "70 families have received stoves." Installing the stoves is part of a missionary program in Guatemala focused on healthcare, literacy, sanitation, and construction improvements to strengthen community infrastructure. The full-time mission staff includes a Guatemalan dentist, physician, and social worker.

Paulsrud, his wife, and other members of the Zionsville congregation are part of an effort by the United Methodist Church's [Mission Guatemala](#) and other non-governmental organizations. The group documented their public health prevention efforts with photos by Paulsrud that tell the story of how NIEHS research can lead to meaningful change on the front lines of global public health.



*Like millions of households worldwide, before receiving their new cookstove, this family prepared meals over a poorly vented open fire. NIEHS research has linked air pollution from open fires, such as this one, to an increase in respiratory and other preventable disease. (Photo courtesy of John Paulsrud)*



*The children of this indigenous Mayan family spent much of their time with their mother as she cooked, which meant they, too, were exposed to potentially harmful levels of particulate matter from incomplete combustion. (Photo courtesy of John Paulsrud)*



*Mission Guatemala volunteers assemble the stove by lifting precast concrete pieces into place. (Photo courtesy of John Paulsrud)*



*The final steps of the process involve venting the smoke to the outside and sealing gaps between parts of the new stove. (Photo courtesy of John Paulsrud)*



*The extended family can now look forward to cleaner air and cleaner walls in their Guatemalan home. The new stove is also more efficient, which can translate into less time and effort spent gathering fuel. (Photo courtesy of John Paulsrud)*

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# Science Notebook

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## 2011 papers of the year

*By Ian Thomas*

Of the nearly 3,000 papers published by NIEHS-supported researchers in 2011, 23 publications were chosen as papers of the year.

### Extramural papers of the year

- Amyloid-binding compound extends lifespan in *C. elegans*
- Mitochondrial, but not nuclear, Ligase3 is required for cellular viability
- Rapid evolution in Hudson River tomcod
- Sperm may be harmed by BPA exposure
- Less toxic and more effective carbon nanotubes for drug delivery
- DNA damage mapped out
- Autism and prenatal vitamins
- Mitochondrial dysfunction in children with autism

### Intramural papers of the year

- Mutations resulting from subtle chemical “trickery”
- Innate immunity linked to DNA damage response
- NIEHS study investigates the impact of poised RNA polymerase II on neuronal gene transcription
- A novel mechanism that may underlie learning and memory
- Two point mutations may influence the efficacy of breast cancer treatment
- Aprataxin structure links DNA repair mechanism to neurodegenerative disease
- IL-35 production by regulatory T cells reverses allergic asthma
- Overcoming phosphate congestion in high energy signaling molecules

### NTP papers of the year

- Global gene profiling in mice: similarities in the molecular landscape with human liver cancer
- Chemical genomics profiling of environmental chemical modulation of human nuclear receptors
- Gene expression alterations in immune system pathways in the thymus after exposure to immunosuppressive chemicals

- Genomic biomarkers of phthalate-induced male reproductive developmental toxicity: A targeted rtPCR array approach for defining relative potency
- *Aloe vera* non-decolorized whole leaf extract-induced tumors in rats share similar molecular pathways with human sporadic colorectal tumors
- Voluntary exercise protects hippocampal neurons from trimethyltin injury
- Prenatal perfluorooctanoic acid exposure in CD-1 mice: low-dose developmental effects and internal dosimetry

## Extramural papers of the year

### **Amyloid-binding compound extends lifespan in *C. elegans***

NIEHS-supported researchers at the Buck Institute for Research on Aging report that a chemical dye that lights up amyloid protein clumps characteristic of Alzheimer's disease also slows aging in the nematode, *C. elegans*. The lifespan-boosting effects of the dye, called Thioflavin T (ThT) or Basic Yellow 1, support the idea that the buildup of misshapen proteins is one of the fundamental events in the aging process. Using roundworms, researchers found that optimum doses of ThT reversed the effects of mutations that cause muscle proteins to misfold and become paralyzed at a particular temperature. The team also found that worms that lack genes important to dealing with misshapen proteins do not live longer when fed ThT.

*Citation:* Alavez S, Vantipalli MC, Zucker DJ, Klang IM, Lithgow GJ. 2011. Amyloid-binding compounds maintain protein homeostasis during ageing and extend lifespan. *Nature* 472(7342):226-229.

[\[abstract\]](#) [\[synopsis\]](#)

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### **Mitochondrial, but not nuclear, Ligase3 is required for cellular viability**

A multi-institutional team of scientists has determined that mitochondrial DNA ligase III (Lig3), an enzyme involved in various DNA repair pathways, is necessary for cellular growth and viability, as compared to the nuclear version of the enzyme. These findings were made through a series of experiments that incorporated various forms of the gene coding for Lig3 in mouse embryonic stem cells. This approach enabled them to determine that mitochondrial Lig3, but not nuclear Lig3, is necessary for cell viability. They also found that substitution of Lig1 for Lig3 in the mitochondria maintains cellular viability.

*Citation:* Simsek D, Furda A, Gao Y, Artus J, Brunet E, Hadjantonakis AK, Van Houten B, Shuman S, McKinnon PJ, Jasin M. 2011. Crucial role for DNA ligase III in mitochondria but not in Xrcc1-dependent repair. *Nature* 471(7337):245-248.

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## Rapid evolution in Hudson River tomcod

New research findings by NIEHS grantees suggest that Hudson River tomcod have undergone rapid evolution, in response to industrial contamination of the river with polychlorinated biphenyls over the last 50 years. Investigators found changes in the gene that codes for the aryl hydrocarbon receptor 2 (AHR2), which mediates toxicity in early life stages. Because the Hudson River fish is resistant to the toxic effects of PCBs, they are able to accumulate more of the chemical, which is then transferred further up the food chain through the larger fish that consume them.

*Citation:* Wirgin I, Roy NK, Loftus M, Chambers RC, Franks DG, Hahn ME. 2011. Mechanistic basis of resistance to PCBs in Atlantic tomcod from the Hudson River. *Science* 331(6022):1322-1325.

[\[abstract\]](#) [\[synopsis\]](#) [\[story\]](#)

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## Sperm may be harmed by BPA exposure

Researchers have found that urinary concentrations of bisphenol A (BPA) may be related to decreased sperm quality and concentration. The study included 190 men and measured sperm concentration, motility, shape, and DNA damage in semen samples from the participants. BPA was detected in 89 percent of the men's urine samples. Sperm concentration was about 23 percent lower in men in the top quartile of exposure, as compared with the lowest quartile. The highest exposed men also had about 10 percent more damaged sperm than the lowest exposed group.

These findings are consistent with previous research, though investigators are continuing this study with a larger cohort to confirm their findings.

*Citation:* Meeker JD, Ehrlich S, Toth TL, Wright DL, Calafat AM, Trisini AT, Ye X, Hauser R. 2010. Semen quality and sperm DNA damage in relation to urinary bisphenol A among men from an infertility clinic. *Reprod Toxicol* 30(4):532-539.

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## Less toxic and more effective carbon nanotubes for drug delivery

Investigators have found that single-walled carbon nanotubes treated with polyethylene glycol (PEG) make more effective and less toxic drug delivery vehicles than untreated nanotubes. The researchers layered carbon nanotubes with PEG, which has been shown to improve their dispersion in aqueous solutions. Both PEG-treated and untreated nanotubes were then incubated with the chemotherapeutic drug cisplatin and injected into laboratory mice. Untreated nanotubes were found to clump together in lung tissue, while PEG-treated nanotubes showed little or no accumulation.

These results give further credence to the use of drug delivery systems utilizing single-walled carbon nanotubes.

*Citation:* Bhirde AA, Patel S, Sousa AA, Patel V, Molinolo AA, Ji Y, Leapman RD, Gutkind JS, Rusling JF. 2010. Distribution and clearance of PEG-single-walled carbon nanotube cancer drug delivery vehicles in mice. *Nanomedicine (Lond)* 5(10):1535-1546.

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## DNA damage mapped out

Using differential epistasis maps, researchers have documented how a cellular genetic network is completely reorganized in response to DNA damaging agents. To achieve this, scientists focused on 400 genes that govern signal transduction pathways in yeast. The map was created by identifying gene interactions before and after exposure to a DNA-damaging agent, similar to compounds used in chemotherapy. Surprisingly, they found that most of the interactions identified after drug exposure were not present without the exposure, leading them to believe that the genetic network was completely reprogrammed by DNA damage.

This discovery represents a new frontier in probing dynamic interactions that enable cells to survive and thrive in varying environmental and genetic contexts.

*Citation:* Bandyopadhyay S, Mehta M, Kuo D, Sung MK, Chuang R, Jaehnig EJ, Bodenmiller B, Licon K, Copeland W, Shales M, Fiedler D, Dutkowski J, Guenole A, van Attikum H, Shokat KM, Kolodner RD, Huh WK, Aebersold R, Keogh MC, Krogan NJ, Ideker T. 2010. Rewiring of genetic networks in response to DNA damage. *Science* 330(6009):1385-1389.

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## Autism and prenatal vitamins

In a study of 566 subjects, comparing a group of autistic children to a control group of normally developed children, researchers found that mothers who didn't take prenatal vitamins were at greater risk of having an autistic child.

Researchers examined maternal intake of prenatal vitamins in the three months before conception and the first month of pregnancy, and they looked for genotypes associated with autism. In addition to finding a distinct dose/response relationship, scientists found that the odds ratio for autism risk in mothers who took prenatal vitamins was 1.8, whereas mothers who didn't take vitamins faced a noticeably higher risk at 7.2. This suggests that the maternal-fetal environment can magnify the effects of a susceptibility gene.

*Citation:* Citation: Schmidt RJ, Hansen RL, Hartiala J, Allayee H, Schmidt LC, Tancredi DJ, Tassone F, Hertz-Picciotto I. 2011. Prenatal vitamins, one-carbon metabolism gene variants, and risk for autism. *Epidemiology* 22(4):476-485.

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## Mitochondrial dysfunction in children with autism

In this study, the investigators propose that mitochondrial deficiencies in brain cells might lead to some of the cognitive impairments associated with autism. While the study does not identify an actual cause of autism, it does suggest that cumulative damage and oxidative stress in mitochondria could influence both the onset and severity of the disorder. Although the study included only 10 autistic children and 10 age-matched controls, its findings may eventually lead to new insights on early diagnosis, treatment, and prevention efforts, though larger studies are necessary moving forward.

*Citation:* Giulivi C, Zhang YF, Omanska-Klusek A, Ross-Inta C, Wong S, Hertz-Picciotto I, Tassone F, Pessah IN. 2010. Mitochondrial dysfunction in autism. *JAMA* 304(21):2389-2396.

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## Intramural papers of the year

### Mutations resulting from subtle chemical “trickery”

When Watson and Crick first described the structure of the DNA helix in 1953, they proposed that mutations might result from mismatches whose geometry mimics that of correct base pairs. This paper provides the first direct structural evidence for this idea, and reveals how the chemical complexity of genetic information can sometimes trick even a normal, healthy cell into making a mistake, for good, enabling evolution, or bad, resulting in disease. It is an example of environmental health science research that fits beautifully into Pillar 1, fundamental research, in the emerging NIEHS strategic plan. We need to understand how things work under normal circumstances if we ever hope to really understand the consequences of environment stress.

*Citation:* Bebenek K, Pedersen LC, Kunkel TA. 2011. Replication infidelity via a mismatch with Watson-Crick geometry. *Proc Natl Acad Sci U S A* 108(5):1862-1867.

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### Innate immunity linked to DNA damage response

This study, the first to come out of the new NIEHS Clinical Research Unit, reveals a strong link, in human subjects, between chromosome lesions that can be induced by environmental agents, the immune-induced inflammatory response, and individual susceptibility. The investigators demonstrated that most of the Toll-like receptor (TLR) family of innate immune genes, which deal with infectious agents in responsive to DNA damage, are directly regulated by the tumor suppressor p53, and they identified the first functional consequences of a SNP in the TLR8 promoter. These findings on individual differences in TLR induction by p53 activation and DNA damage should prove useful in the development of TLR-targeted vaccines and TLR-based cancer treatments.

*Citation:* Menendez D\*, Shatz M\*, Azzam K, Garantziotis S, Fessler MB, Resnick MA. 2011. The Toll-like receptor gene family is integrated into human DNA damage and p53 networks. PLoS Genet 7(3):e1001360. (\*co-first authors).

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## **NIEHS study investigates the impact of poised RNA polymerase II on neuronal gene transcription**

Activity-dependent plasticity of synapses is an important process in the development of brain circuitry, a time when the brain is susceptible to environmental insults. Rapid activity-dependent induction of genes plays a critical role in consolidating synaptic changes, so an understanding of how this occurs could provide important clues into targets of environmental toxicants.

*Citation:* Saha RN, Wissink EM, Bailey ER, Zhao M, Fargo DC, Hwang JY, Daigle KR, Fenn JD, Adelman K, Dudek SM.. 2011. Rapid activity-induced transcription of Arc and other IEGs relies on poised RNA polymerase II. Nat Neurosci 14(7):848-856.

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## **A novel mechanism that may underlie learning and memory**

Since smoking is suspected to be protective in Alzheimer's disease through action on nicotinic acetylcholine receptors (nAChRs), and drugs acting on these receptors improve cognitive function, the scientists investigated how endogenous acetylcholine acting through nAChRs affected cellular models of learning and memory. The long-term aim of this work is to understand the brain circuits involved in environmental disease and aid in the development of therapeutics to treat these diseases.

*Citation:* Gu Z, Yakel JL. 2011. Timing-dependent septal cholinergic induction of dynamic hippocampal synaptic plasticity. Neuron 71(1):155-165.

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## **Two point mutations may influence the efficacy of breast cancer treatment**

This paper describes the initial development and characterization of a mutant estrogen receptor alpha mouse model that segregates the tissue and physiological functionality of the two transcription activation functions

to certain tissues. Endocrine disrupting chemicals (EDCs) activate this mutant through the AF-1 similar to Tamoxifen and will allow assessment of the EDC tissue selective mechanism of action.

*Citation:* Arao Y, Hamilton KJ, Ray MK, Scott G, Mishina Y, Korach KS. 2011. Estrogen receptor alpha AF-2 mutation results in antagonist reversal and reveals tissue selective function of estrogen receptor modulators. *Proc Natl Acad Sci U S A* 108(36):14986-14991.

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## **Aprataxin structure links DNA repair mechanism to neurodegenerative disease**

Exposure to environmental toxicants and stressors, chronic inflammation, and cellular respiration all contribute to production of oxidative DNA damage, including DNA strand breaks and DNA base damage, that when metabolized, can give rise to cytotoxic 5'-adenylation DNA lesions. This study provides key insights into the chemistry and biology of DNA-5'-adenylation genome repair by aprataxin, and explains how mutations in the human aprataxin gene result in small, but devastating changes to the aprataxin protein shape that underlie the crippling heritable neurodegeneration disease ataxia with oculomotor apraxia 1 (AOA1).

*Citation:* Tumbale P, Appel CD, Kraehenbuehl R, Robertson PD, Williams JS, Krahn J, Ahel I, Williams RS. 2011. Structure of an aprataxin-DNA complex with insights into AOA1 neurodegenerative disease. *Nat Struct Mol Biol* 18(11):1189-1195.

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## **IL-35 production by regulatory T cells reverses allergic asthma**

Some previous studies have shown that the prevalence of allergic asthma is associated with exposure to environmental endotoxin, whereas other studies have shown that endotoxin can protect against the development of asthma. The basis for this apparent paradox has been unclear. This paper shows that although endotoxin can prime T helper 2 (Th2) and Th17 responses to inhaled allergens, it also induces T regulatory (Treg) cell proliferation. The paper further identified a specific type of Treg cell that suppresses allergic responses by producing the recently identified cytokine, IL-35.

*Citation:* Whitehead GS, Wilson RH, Nakano K, Burch LH, Nakano H, Cook DN. 2012. IL-35 production by inducible costimulator (ICOS)-positive regulatory T cells reverses established IL-17-dependent allergic airways disease. *J Allergy Clin Immunol* 129(1):207-215.

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## Overcoming phosphate congestion in high energy signaling molecules

Inositol pyrophosphates regulate the body's metabolic balance, a life-sustaining process that is under constant environmental pressure. Breakdown of metabolic control processes is evident in illnesses such as diabetes, cancer and aging. The rational design of drugs to improve human health is facilitated by the molecular template that is provided by our atomic level description of the structure and reaction mechanism of an enzyme that synthesizes inositol pyrophosphates.

*Citation:* Wang H, Falck JR, Hall TM, Shears, SB. 2011. Structural basis for an inositol pyrophosphate kinase surmounting phosphate crowding. *Nat Chem Biol* 8(1):111-6.

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## NTP papers of the year

### Global gene profiling in mice: similarities in the molecular landscape with human liver cancer

Hepatocellular carcinoma (HCC) is an important cause of morbidity and mortality worldwide. Although the risk factors of human HCC are well known, the molecular pathogenesis of this disease is complex and, in general, treatment options remain poor.

Using global gene expression profiling in the B6C3F1 rodent model, researchers identified the dysregulation of several mediators similarly altered in human HCC, including re-expression of fetal oncogenes, upregulation of protooncogenes, downregulation of tumor suppressor genes, and abnormal expression of cell cycle mediators, growth factors, apoptosis regulators, and angiogenesis and extracellular matrix remodeling factors. These data provide further support for the use of this model in hazard identification of compounds with potential human carcinogenicity risk, and may help in better understanding the mechanisms of tumorigenesis resulting from chemical exposure in the NTP two-year carcinogenicity bioassay.

*Citation:* Hoenerhoff MJ, Pandiri AR, Lahousse SA, Hong HH, Ton TV, Masinde T, Auerbach SS, Gerrish K, Bushel PR, Shockley KR, Peddada SD, Sills RC. 2011. Global gene profiling of spontaneous hepatocellular carcinoma in B6C3F1 mice: similarities in the molecular landscape with human liver cancer. *Toxicol Pathol* 39(4):678-699.

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# Chemical genomics profiling of environmental chemical modulation of human nuclear receptors

In response to the growing demand for more efficient and cost-effective means of assessing environmental chemical toxicity, the U.S. Tox21 program has proposed a number of alternative strategies for toxicity testing and data screening. The goal of this study was to develop methods to evaluate the data generated from these assays, to guide future assay selection and prioritization.

By examining roughly 3,000 environmental chemicals against a panel of 10 human nuclear receptors for reproducibility, scientists determined the assays to be appropriate in terms of biological relevance. They were also able to formulate data-driven strategies for discriminating true signals from artifacts and to prioritize assays based on data quality.

*Citation:* Huang R, Xia M, Cho MH, Sakamuru S, Shinn P, Houck KA, Dix DJ, Judson RS, Witt KL, Kavlock RJ, Tice RR, Austin CP. 2011. Chemical genomics profiling of environmental chemical modulation of human nuclear receptors. *Environ Health Perspect* 119(8):1142-1148.

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# Gene expression alterations in immune system pathways in the thymus after exposure to immunosuppressive chemicals

Dysregulation of positive and negative selection, antigen presentation, or apoptosis in the thymus can lead to immunosuppression or autoimmunity. This study hypothesized that genomic analysis of thymus after chemical-induced atrophy would yield transcriptional profiles that suggest pathways of toxicity associated with reduced function.

By exposing rodents to four immunosuppressive agents and evaluating changes in gene expression, investigators found that all four chemicals induced thymic atrophy and changes in both the relative proportion and absolute number of CD3(+), CD4(+)/CD8(-), CD4(-)/CD8(+), and CD4(+)/CD8(+) thymocytes.

Genomic analysis revealed gene expression changes in several pathways that are commonly associated with xenobiotic-induced immune system perturbations, particularly those that contribute to the development and maturation of thymic T cells.

*Citation:* Frawley R, White K Jr, Brown R, Musgrove D, Walker N, Germolec D. 2011. Gene expression alterations in immune system pathways in the thymus after exposure to immunosuppressive chemicals. *Environ Health Perspect* 119(3):371-376.

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## **Genomic biomarkers of phthalate-induced male reproductive developmental toxicity: A targeted rtPCR array approach for defining relative potency**

Male rat fetuses exposed to certain phthalate esters (PEs) during sexual differentiation display reproductive tract malformations due to reductions in testosterone (T) production and the expression of steroidogenesis- and INSL3-related genes. In the current study, researchers examined key target genes representing sexual determination and differentiation, steroidogenesis, gubernaculum development, and androgen signaling pathways to rank the relative potency of several PEs.

Despite speculation of PPAR involvement in the effects of PEs on the fetal testis, no PPAR-related genes were affected in the fetal testes by exposure to any of the tested PEs. Furthermore, the potent PPARalpha agonist, WY-14643, did not reduce fetal testicular T production following GD 14-18 exposure, suggesting that the anti-androgenic activity of PEs is not PPARalpha-mediated.

*Citation:* Hannas BR, Lambricht CS, Furr J, Evans N, Foster PM, Gray LE, Wilson VS. 2011. Genomic biomarkers of phthalate-induced male reproductive developmental toxicity: A targeted rtPCR array approach for defining relative potency. *Toxicol Sci*; doi 10.1093/toxsci/kfr315 [Online 22 November 2011].

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## ***Aloe vera* non-decolorized whole leaf extract-induced tumors in rats share similar molecular pathways with human sporadic colorectal tumors**

Research by NTP and the National Center for Toxicological Research has demonstrated a dose-dependent increase in large intestinal tumors in F344 rats chronically exposed to *Aloe barbadensis* Miller (*Aloe vera*) non-decolorized whole leaf extract (AVNWLE) in drinking water.

The morphological and molecular pathways of these tumors were then compared to human colorectal cancer (hCRC) literature. Histological evaluation of the large intestinal tumors indicated eight of twelve adenomas (Ads) and four of twelve carcinomas (Cas). Mutation analysis of eight Ads and four Cas identified point mutations in exons 1 and 2 of the *Kras* gene (two of eight Ads, two of four Cas), and in exon 2 of the *Ctnnb1* gene (three of eight Ads, one of four Cas). In conclusion, the AVNWLE-induced large intestinal tumors in F344 rats share several similarities with hCRC at the morphological and molecular levels.

*Citation:* Pandiri AR, Sills RC, Hoenerhoff MJ, Peddada SD, Ton TV, Hong HH, Flake GP, Malarkey DE, Olson GR, Pogribny IP, Walker NJ, Boudreau MD. 2011. *Aloe vera* non-decolorized whole leaf extract-induced large intestinal tumors in F344 rats share similar molecular pathways with human sporadic colorectal tumors. *Toxicol Pathol* 39(7):1065-1074.

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## **Voluntary exercise protects hippocampal neurons from trimethyltin injury**

In the periphery, exercise induces interleukin (IL)-6 to downregulate tumor necrosis factor (TNF), elevate interleukin-1 receptor antagonist (IL-1RA), decreasing inflammation. IL-6 production in the hippocampus following exercise suggests the potential of a similar protective role as in the periphery to down-regulate TNFalpha and inflammation.

Using a chemical-induced model of hippocampal dentate granule cell death dependent upon TNF receptor signaling, researchers demonstrated neuroprotection in mice with two weeks access to running wheel. In IL-6 deficient mice, exercise did not attenuate trimethyltin-induced tremor and a diminished level of neuroprotection was observed. These data suggest a contributory role for IL-6 induced by exercise for neuroprotection in the CNS similar to that seen in the periphery.

*Citation:* Funk JA, Gohlke J, Kraft AD, McPherson CA, Collins JB, Jean Harry G. 2011. Voluntary exercise protects hippocampal neurons from trimethyltin injury: possible role of interleukin-6 to modulate tumor necrosis factor receptor-mediated neurotoxicity. *Brain Behav Immun* 1063-1077.

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## **Prenatal perfluorooctanoic acid exposure in CD-1 mice: low-dose developmental effects and internal dosimetry**

To investigate the low-dose effects of perfluorooctanoic acid (PFOA) on offspring, timed-pregnant CD-1 mice were gavaged with PFOA for all or half of gestation. In both studies, the offspring of all PFOA-treated dams exhibited significantly stunted mammary epithelial growth as assessed by developmental scoring.

Evaluation of internal dosimetry in offspring revealed that PFOA concentrations remained elevated in liver and serum for up to six weeks and that brain concentrations were low and undetectable after four weeks. Also, PFOA-induced effects on mammary tissue occurred at lower doses than effects on liver weight in CD-1 mice and persisted until 12 weeks of age following full-gestational exposure.

*Citation:* Macon MB, Villanueva LR, Tatum-Gibbs K, Zehr RD, Strynar MJ, Stanko JP, White SS, Helfant L, Fenton SE. 2011. Prenatal perfluorooctanoic acid exposure in CD-1 mice: low-dose developmental effects and internal dosimetry. *Toxicol Sci* 122(1):134-145.

[\[abstract\]](#)

(Ian Thomas is a public affairs specialist with the NIEHS Office of Communications and Public Liaison, and a regular contributor to the Environmental Factor.)

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# Distinguished lecturer discusses the mechanism of action of amphetamine

By Anshul Pandya

Neuroscientist Susan Amara, Ph.D., delivered the latest talk in the NIEHS Distinguished Lecture Series Dec. 13, 2011, with a presentation focused on the mechanism of action of amphetamine on the dopamine and glutamate transporters. These transporters are responsible for the clearance of the neurotransmitters dopamine and glutamate following their release at sites of neuronal communication in the nervous system known as synapses.

Amara specializes in the structure and function of brain neurotransmitter transporter proteins and is the Thomas Detre professor and chair of neurobiology at the University of Pittsburgh. She is also the most recent past president of the Society for Neuroscience, the largest organization of neuroscientists in the world. NIEHS lead researcher [Jerrel Yakel, Ph.D.](#), hosted the talk.

Her current research is focused on elucidating the biochemical pathways that mediate dopamine transporter internalization by amphetamine. Understanding this mechanism is important because the dopamine transporter serves as a target for a variety of clinically used medications and recreationally abused drugs.

## The actions of amphetamine

“While reuptake inhibitors of serotonin, norepinephrine, and dopamine are widely used clinically to treat depression,” Amara said, “we know much less about the mechanism of action of amphetamines, which also target the three biogenic amine transport systems.” In her talk, Amara stressed that cocaine and amphetamines, both commonly abused psychostimulants, have different actions on the dopamine transporter.

Cocaine inhibits the dopamine transporter at the cell surface, whereas amphetamine, in addition to being an inhibitor of the dopamine transporter, enters the neurons. Amara’s research has found that once it enters neuronal cytoplasm, amphetamine activates intracellular signaling pathways and causes the internalization of the dopamine transporter.



*“The key is to understand the functioning of the transporters of neurotransmitters in the brain, so that they can be targeted by new drugs to treat psychiatric disorders,” Amara said. (Photo courtesy of Steve McCaw)*



*Amara engaged the audience with intriguing information about the action of amphetamine on a cellular level and the pathways involved. (Photo courtesy of Steve McCaw)*

Near the end of her talk, Amara described the action of amphetamine on a neuronal glutamate transporter. Similar to its effect on the dopamine transporter, amphetamine also causes the internalization of the glutamate transporter. She went on to show experimental data suggesting that in order for amphetamine to mediate the internalization of the glutamate transporter, the transporter requires a particular stretch of five amino acids that are located in the C-terminus or near the end of its protein structure. Removing these amino acids blocks glutamate transporter internalization by amphetamine.



*Amara and Yakel listened to questions raised by audience members after the talk. (Photo courtesy of Steve McCaw)*

### **Interaction with NIEHS postdocs**

After her lecture, Amara joined NIEHS postdoctoral fellows for a brown bag lunch. It was an opportunity for these young scientists to tell Amara about their own research interests and seek her advice regarding their careers. Amara briefly spoke about her research and career progression, and about the prospects of research funding for biomedical science in the current budgetary environment. She also mentioned her lobbying effort with Congress during her tenure as the president of the Society for Neuroscience, in favor of keeping research funding at current levels.

(Anshul Pandya, Ph.D., is an Intramural Research Training Award (IRTA) fellow in the NIEHS Laboratory of Neurobiology Ion Channel Physiology Group.)

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*Audience members listened to the Amara talk with keen interest. From right to left, Thomas McCormack, Ph.D., Christian Erxleben, Ph.D., Ezequiel Marron, Ph.D., Bernd Gloss, Ph.D., Erica Scappini and Fengxia Mizuno, Ph.D. (Photo courtesy of Steve McCaw)*

## **NIEHS selects 2012 ONES awardees**

*By Eddy Ball*

NIEHS has announced funding for seven early stage tenure-track investigators as 2012 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.

The new awardees reflect the broad range of NIEHS research interests.

- [Lauren Aleksunes, Pharm.D., Ph.D.](#), an assistant professor in the Ernest Mario School of Pharmacy Department of Pharmacology and Toxicology at Rutgers, The State University of New Jersey

- **Ulrike Dydak, Ph.D.**, an assistant professor of health sciences in the Purdue University School of Health Sciences, with an adjunct appointment at the Indiana Institute for Biomedical Imaging Sciences at Indiana University School of Medicine
- **Stacey Harper, Ph.D.**, an assistant professor of Chemical Engineering in the Oregon State University School of Chemical, Biological, and Environmental Engineering
- **Joel Meyer, Ph.D.**, an assistant professor of environmental toxicology in the Duke University Nicholas School of the Environment
- **Brandon Pierce, Ph.D.**, an assistant professor of epidemiology in The University of Chicago Department of Health Studies
- **Christy Porucznik, Ph.D.**, an assistant professor in the University of Utah School of Medicine Public Health Program
- **Vishal Vaidya, Ph.D.**, an assistant professor of medicine and environmental health at Harvard Medical School and the Harvard School of Public Health

“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.”



*A former NIEHS-supported postdoc at The University of Kansas Medical Center in the lab of Curtis Klaassen, Ph.D., Aleksunes will pursue her studies on the disposition of environmental chemicals during pregnancy. (Photo courtesy of Rutgers University)*



*A physicist who focuses on the investigation of human in vivo metabolism, Dydak will utilize neuroimaging for early diagnosis of manganese toxicity in humans and rodents, expanding on preliminary research funded through an NIEHS exploratory grant. (Photo courtesy of Purdue University)*



*A former postdoc in the NIEHS-funded Environmental Health Sciences Center at Oregon State University, Harper plans to conduct integrative studies to define drivers of nanomaterial toxicity. (Photo courtesy of Stacey Harper)*



*A former postdoc in the NIEHS Laboratory of Molecular Genetics, Meyer will expand his investigation of the role of mitochondrial DNA damage in neurodegeneration. (Photo courtesy of Duke University)*



*Partially supported by an NIEHS Superfund Research Program grant during his postdoc, Pierce will continue research with a Bangladesh cohort, studying [the effects of arsenic exposure on telomeres](#). (Photo courtesy of Brandon Pierce)*



*A former lieutenant commander in the United States Public Health Service, who was supported by an NIEHS training grant during graduate school, Porucznik will [investigate peri-conceptional biomonitors](#) as part of her interests in preventive medicine. (Photo courtesy of Christy Porucznik)*



*A recipient of an NIEHS Pathway to Independence Award in 2007, and former summer intern at NIEHS during graduate school, Vaidya will study [fibrinogen signaling in kidney tissue repair](#). (Photo courtesy of Vishal Vaidya)*

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## Researchers find potential new avenue for cancer therapies

*By Robin Arnette*

Recent findings in mice suggest that blocking the production of small molecules produced in the body, known as epoxyeicosatrienoic acids (EETs), may offer a novel strategy for treating cancer by eliminating the blood vessels that feed tumors. This research is the first to show that EETs work in concert with vascular endothelial growth factor (VEGF), a protein known to induce blood vessel growth. Together, EETs and VEGF promote metastasis, or the spread of cancer, by encouraging the growth of blood vessels that supply nutrients to cancer cells.

The research team, comprised of scientists from NIEHS and several other institutions, published its [data](#) online in the Dec. 19 issue of *The Journal of Clinical Investigation*.

### **EETs, a double-edged sword in health and disease**

Preclinical research suggests that patients with a variety of vascular conditions, such as diabetes, hypertension, inflammation, stroke, and heart attack, may benefit by increasing their EET levels, because the compounds cause blood vessels to dilate, and reduce tissue inflammation and cell death. However, previous work has also demonstrated that EETs make tumor cells grow faster, and cause them to migrate and become metastatic. [Darryl Zeldin, M.D.](#), NIEHS scientific director and author on the paper, said he believed that human metabolism has to achieve a certain harmony in regard to EETs.

“The body has to produce enough EETs to maintain a healthy cardiovascular system without promoting cancer. It has to balance the double-edged sword just right,” Zeldin said.

To find out how EETs encourage the development of cancer, the team created two mice strains, one with high levels of EETs and one with low levels of EETs.

“The mice with higher EETs developed more metastatic tumors compared to the mice with lower EETs,” Zeldin said. “Often, the tumor itself will produce more EETs, which can speed up tumor growth and its subsequent spread, but our analysis demonstrated that the EETs produced by the surrounding tissues encouraged tumor growth and migration.”

**Matthew Edin, Ph.D.**, a research fellow in Zeldin’s group, is one of the authors on the paper and helped develop the mice strains. He said EETs directly lead to the creation of new blood vessels, also known as angiogenesis, which the cancer cells need in order to receive oxygen and nutrients to grow. He equated the process to what happens when a builder begins constructing a new housing development.

“One of the first things construction crews have to do is build the roads, so that materials and workers can be transported to the site,” Edin said. “In cancer, EETs accelerate the road building, allowing the housing development to expand quickly.”

### **Maintaining balance with an experimental antagonist**

According to Dipak Panigrahy, M.D., an author on the paper and a research associate at the Dana-Farber/Children’s Hospital Cancer Center, Boston, EETs have a potent stimulatory effect, promoting cancer growth and metastasis, a process that could be effectively inhibited using novel antagonists, such as EEZE, which are compounds that interfere with this pathway in mice. EEZE has not been approved for human use, and is only used for research.

“EEZE is structurally similar to EETs, but it blocks the effect of EETs and dramatically slows tumorigenesis,” Panigrahy explained.

Mark Kieran, M.D., Ph.D., another author of this collaborative study and also from Dana-Farber, commented on the importance of the research.

“The identification of an old pathway studied for many years in cardiovascular disease has found a new role in regulating cancer growth and metastasis, the primary causes of cancer related deaths,” he said. “With these findings, opportunities to better understand the underlying mechanisms that drive cancer, and thus the development of effective therapies for their treatment, moves one step closer to a reality.”



*In addition to his role as scientific director, Zeldin heads the [Molecular and Cellular Biology Group](#) and [Environmental Cardiopulmonary Disease Group](#) in the NIEHS Laboratory of Respiratory Biology. (Photo courtesy of Steve McCaw)*



*Edin was second author on the 31-member team of researchers. (Photo courtesy of Steve McCaw)*

*Citation:* Panigrahy D, Edin ML, Lee CR, Huang S, Bielenberg DR, Butterfield CE, Barnes CM, Mammoto A, Mammoto T, Luria A, Benny O, Chaponis DM, Dudley AC, Greene ER, Vergilio JA, Pietramaggiore G, Scherer-Pietramaggiore SS, Short SM, Seth M, Lih FB, Tomer KB, Yang J, Schwendener RA, Hammock BD, Falck JR, Manthathi VL, Ingber DE, Kaipainen A, D'Amore PA, Kieran MW, Zeldin DC. 2011. Epoxyeicosanoids stimulate multiorgan metastasis and tumor dormancy escape in mice. *J Clin Invest*; doi:10.1172/JCI58128 [Online 19 December 2011].

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## Seminar explores the potential of bioinformatics in autism research

By Ian Thomas

Autism experts from around the country gathered Nov. 29-30 at the Marriott in Research Triangle Park, N.C., for a two-day discussion sponsored by NIEHS on bioinformatics and its role in autism research. Focusing on the genetic and environmental causes, the group outlined a number of cutting-edge techniques for taking advantage of leading-edge computational and screening approaches to share information, generate new hypotheses, and expand the existing knowledge base surrounding autism spectrum disorders (ASD).

“At present, NIEHS commits roughly \$7 million a year to autism research and, while we’ve made some great progress in recent years, we need to do more,” said NIEHS/NTP Director [Linda Birnbaum, Ph.D.](#), a member of the U.S. Department of Health and Human Services’ [Interagency Autism Coordinating Committee](#). “According to the latest figures from the CDC [Centers for Disease Control and Prevention], nearly 1 in 100 kids are affected by autism. Meetings like this help us work toward the goal of more effective treatment and prevention.”



*Birnbaum noted that autism cases among boys outnumber those of girls, 4 to 1. (Photo courtesy of Steve McCaw)*

### When genes and the environment collide

A major theme throughout the event was that, while genetic and environmental factors must always be studied individually, it is the combined influence of both that could prove vital to discovering new methods of treatment and prevention.

“All too often in autism research, the genetic viewpoint is seen as a competitor to the environmental viewpoint when it comes to causation,” said Cindy Lawler, Ph.D., a scientific program administrator for the [NIEHS Centers for Children’s Environmental Health and Disease Prevention Research](#). “Our goal for this meeting was to bring members of both sides together in the hopes of fostering a greater understanding, so that one can actually inform the other, rather than eclipse it.”

Further complicating the matter is the misperception that autism is a singular disease, Lawler added.

“It’s key to remember that autism is actually a group of neurodevelopmental disorders,” said Autism Speaks’ Chief Science Officer [Geraldine Dawson, Ph.D.](#) “Even though each disorder contains the same three core symptoms — social impairment, communication impairment, and restricted range of activities — it’s important

to recognize that this condition involves multiple influences and etiologies, with environmental factors being one piece of this complex puzzle.”

### The technological edge

Bioinformatics is the application of computer and information technology to analyze, dissect, and catalog biological data for the purposes of formulating and testing new scientific hypotheses. This involves the use of numerous informatics resources, such as databases, modeling and imaging programs, and data mining software, among others.

“All of the information contained in our database comes directly from the scientific literature itself,” said Allan Peter Davis, Ph.D., project manager for the [Comparative Toxicogenomics Database](#), which is funded in part by NIEHS. “So, for instance, if a scientist has a question about a particular gene-disease relationship, he or she can simply track that piece of data back to the original source material.”

Still, Davis and others agree that automated statistics can only go so far.

“We hire professional Ph.D. curators who do nothing but read these papers and look specifically for chemical-gene-disease interactions, which are then formatted and cataloged into the database. This human element is crucial because it helps to eliminate a lot of the factual ambiguities that basic text mining tends to create,” he said.

### A complex approach for a complex problem

“Our number one focus at NIEHS has always been on prevention,” said Birnbaum. “As we all know, autism is a complex group of disorders, which will require complex approaches in order to better understand. Bioinformatics is one such tool that allows us to do that.”

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

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*Dawson outlined Autism Speaks' ongoing commitment to genetic and environmental health research. (Photo courtesy of Steve McCaw)*



*Leading minds from the genetic, environmental, and technological fields listened as speakers discuss the collective impact of all three on public health, including Autism Speaks' Dusan Bosnjakovic, center, and NIEHS grantee Heather Volk, Ph.D., right. (Photo courtesy of Steve McCaw)*

# Kleckner offers glimpses inside a living *E. coli* cell

By Jeffrey Stumpf

During a Nov. 21 seminar at NIEHS, molecular biologist Nancy Kleckner, Ph.D., bypassed decades of her own groundbreaking research in the biology of prokaryotic transposons and meiosis, to focus on recent exciting work in the physical biology of chromosomes. Hosted by NIEHS postdoctoral fellow [Richard Gradman, Ph.D.](#), Kleckner spoke as part of the Laboratory of Molecular Genetics (LMG) Fellows Invited Lecture series.

[Kleckner](#), the Herchel Smith Professor of Molecular Biology at Harvard University, entertained the NIEHS audience with stunning images of dynamically changing chromosomes in cells of the model bacteria *E. coli*. While DNA research mostly focuses on molecules that affect basic processes in maintenance, replication, and repair, Kleckner provided a different angle with research describing how physical and mechanical forces might underlie chromosome behavior and function.

## Stress and stress relief could explain the even spacing of meiotic crossovers

Correctly assuming an audience of physics novices, Kleckner provided the following example. Pulling on a rubber band will cause it to come under tension to produce what is called tensile stress. Cutting the rubber band will alleviate that stress not only at the point of the cut, but also along the length of the rubber band, a phenomenon termed redistribution of stress. The same principle will apply analogously to imposition and relief of pushing or compression stress. This principle, Kleckner argues, could underlie the even distribution of crossover events that occur during meiosis.

“All mechanical systems include such redistribution of stress, which in effect provides a method of communication,” Kleckner remarked. “Even spacing of the crossover events requires communication along the chromosome, because the positions of these events are not genetically specified. Instead, occurrence of an event at one position intrinsically disfavors the occurrence of another event nearby.”

If the site of a crossover is determined by a stress-promoted process, the result will be reduction of stress locally, resulting in reduced probability of another nearby crossover.

Crossover events during meiosis are required for segregation of meiotic chromosomes. Defects in crossing over, or their distribution along chromosomes, can lead to nondisjunction, the improper separation of chromosomes to gametes. Thus, considerations of how crossover events are located may be important in studying nondisjunction in humans. Kleckner mentioned that the nondisjunction rate in human cells can be up to 10 percent, but admits that studying the many causes for nondisjunction represents what she described as a whole other line of work.



LMG fellows invited guest lecturer Nancy Kleckner (Photo courtesy of Nancy Kleckner)



Gradman is a member of the LMG Spontaneous Mutation and DNA Repair Group. (Photo courtesy of Steve McCaw)

## The tangled web that cells weave

Questioning the possibility of an organized shape of the DNA of bacterial chromosomes, called nucleoids, Kleckner showed images of nucleoids captured by epifluorescence microscopy. Time lapsed images demonstrated that DNA in *E. coli* maintains a dynamic shape described as a helical ellipsoid, which can be either left-handed or right-handed. Kleckner showed videos that showcased how the nucleoids, which have a substructure comprised of dynamic longitudinal bundles, move elegantly as definable objects. “The DNA has a shape,” she joked. “It’s not just a bag of spaghetti.”

So what determines the nucleoid shape in *E. coli*? Kleckner explained part of the answer by means of a concept called radial confinement. Her observations suggest that bacterial cells use shape to separate their chromosomes, as a primordial precursor to the more complicated filamentous network of the mitotic spindle found in eukaryotic cells.

“The nucleoid is an ellipsoid that is longitudinally very stiff or, in technical terms, the persistence length of the ellipsoid is greater than the radius of the cell cylinder,” Kleckner observed. “During DNA replication, this ellipsoid evolves into a helicoidal shape, because it is forced around the cell periphery and held in place by friction, like a rubber rod trapped in a cylinder. As the two sister nucleoids emerge during replication, the stress resulting from this confinement increases until, finally, the two entities force their way into an end-to-end relationship.”

(Jeffrey Stumpf, Ph.D., is a postdoctoral fellow in the NIEHS Laboratory of Molecular Genetics Mitochondrial DNA Replication Group.)

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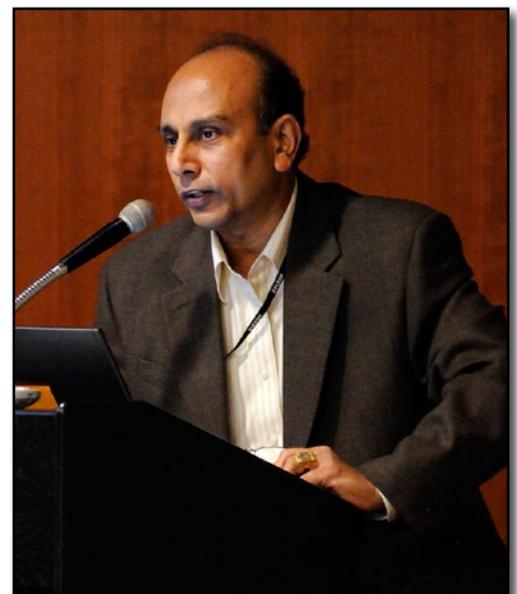
## Holian discusses lung inflammation caused by nanoparticles

*By Jeffrey Stumpf*

Engineered nanomaterials (ENMs) may be small, but their unique properties make them useful for many commercial and medical applications. However, the same properties that make ENMs so useful in the marketplace, also make their interactions with biological systems difficult to anticipate and critically important to explore.

NIEHS grantee [Andrij Holian, Ph.D.](#), a toxicologist and director of the Center for Environmental Health Sciences at The University of Montana, presented the latest results from his experiments on the health and safety aspects of ENMs Dec. 6, as part of the Institute’s Keystone seminar series.

ENMs are generally defined as particles less than 100 nanometers in size, with many different shapes and surface properties. They can be made from numerous materials, including carbon, titanium dioxide, gold, silver, and selenium, and they are used in the manufacture of a rapidly growing range of products. Because of their size and composition, nanoparticles may enter the cell and be unable to be degraded effectively.



*The host of Holian’s talk was NIEHS Health Scientist Administrator Sri Nadadur, Ph.D., who oversees a portfolio of nanomaterials Grand Opportunities grants. (Photo courtesy of Steve McCaw)*

While ENMs, such as crystalline silica have been linked to such diseases as lung fibrosis, others are not active in the cell. “The real challenge is to understand what defines a harmful and benign nanomaterial,” explained Holian. “It is not obvious from the makeup of the material what defines a bioactive material.”

To address the potential danger of nanoparticles to human health, Holian exposed lung epithelial cells and macrophages to a range of nanomaterials. His series of experiments were part of an effort to determine properties of nanoparticles that cause harm, to identify mechanisms that cause bioactivity, and to discover ways to modify nanoparticles that could improve their safety, while maintaining as much of their utility as possible.

### **In nanoparticle toxicology, size matters**

Holian explained that predicting the potential pathology of these particles is challenging, because of the preponderance of properties that may possibly perturb the cell. Besides the size, shape, and makeup of the material, nanoparticles differ in surface chemistry, charge, and hydrophobicity.

“The changes in the distribution once this material has been inhaled, where it goes in the lung, and how rapidly it disappears is another whole dimension that is layered on top of this field,” remarked Holian.

One experiment Holian described was a comparison of immune responses of macrophages after four hours of exposure to titanium dioxide particles of different shapes, including nanospheres, short nanobelts, and long nanobelts. Unlike the smaller and more spherical counterparts, the long nanobelts caused the greatest inflammatory response and persisted in the lungs for weeks. For Holian, the importance of nanoparticle shape led to comparison to another well-known environmental hazard.

“Clearly, it was the length of nanobelts that was an important determinant of biological outcome,” explained Holian, “similar to long asbestos fibers, which are also the most bioactive.”

Besides size and shape, Holian also studied the biotoxicity of multiwalled carbon nanotubes with different metal contents and surface modifications. He concluded that nickel content increased inflammatory response and cytotoxicity, while adding surface carboxyl groups reduced bioactivity.



*Holian explained that the persistence of ENMs in the body makes them a concern for toxicologists. (Photo courtesy of Steve McCaw)*



*Holian’s talk drew scientists from across the Institute. Shown above is NIEHS Health Scientist Administrator Danielle Carlin, Ph.D., who was one of several attendees from the Institute’s Division of Extramural Research and Training. (Photo courtesy of Steve McCaw)*

## The next step

Addressing the social and economic ramifications of future regulations of nanoparticles, Holian advocated a cautious approach in making conclusions about the safety of ENMs. “We don’t really understand all of the science ourselves [yet] and the last thing we want is a preemptive strike that may not be accurate,” Holian suggested. “But we are preemptively trying to study this [issue of safety]. We need to do this work and share this information with the public.”

Above all, Holian cautioned, “We don’t need another asbestos epidemic.”

Additionally, Holian argued that the future of regulating nanoparticles is an issue weighing the value of ENMs against their risk to human health. “These nanobelts have tremendous value in electronic industries and filtration. If we look at long silver and gold nanowires, I suspect that they all will be bioactive,” Holian postulated. “The goal may be to reduce human exposure, not necessarily to eliminate nanoparticle production.”

(Jeffrey Stumpf, Ph.D., is a postdoctoral fellow in the NIEHS Laboratory of Molecular Genetics Mitochondrial DNA Replication Group.)

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## NTP board moves initiatives forward

*By Ernie Hood*

The NTP Board of Scientific Counselors (BSC) accomplished quite a bit in its Dec. 15, 2011, session at NIEHS. Highlights of the meeting included updates by the NTP director and associate director, three chemical nominations, a hair dye workshop proposal, a report on the NTP diabetes and obesity workshop, and presentation of a proposed review process for the Report on Carcinogens ([see text box](#)).

Before moving into its packed agenda of reports and proposals, the BSC heard from NIEHS/NTP Director Linda Birnbaum, Ph.D., who thanked three departing members for their contributions. Birnbaum presented certificates and letters of appreciation to Mitzi Nagarkatti, Ph.D., Ruthann Rudel, and Gina Solomon, M.D., whose terms expired Dec. 27, 2011.

### Chemical nominations evaluated

The BSC approved NTP research and testing concepts for [three chemicals](#), moving each of them to the next step in the process of being developed into an NTP research program. Two are high production volume (HPV) compounds, while the third is used mainly in laboratory settings and has been implicated in the deaths of two workers.

Sulfolane is a solvent used mainly in natural gas and petroleum refining, with U.S. production in 2006 estimated at 10-50 million pounds. Nominated to the NTP by several agencies and officials from the state of Alaska and the Agency for Toxic Substances and Disease Registry, sulfolane has been detected in nearly 300 drinking



*As she does at each BSC meeting, Birnbaum opened the meeting by updating BSC members on activities at NIEHS since their last gathering. (Photos courtesy of Steve McCaw)*

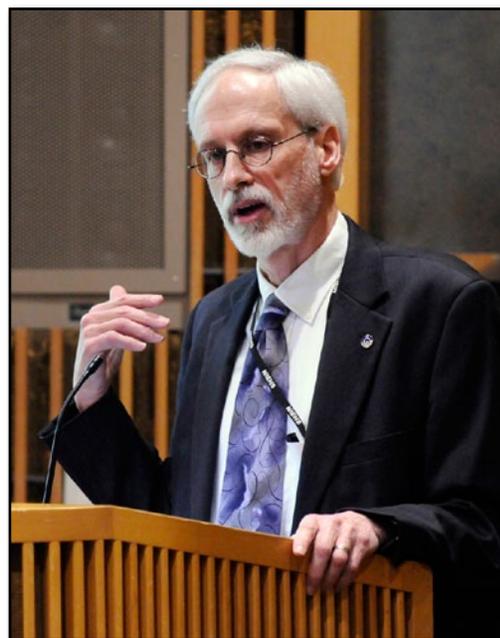
water wells within the town of North Pole, Alaska, possibly as a result of activities at a nearby petroleum refinery. It is also present at other sites within Canada. Sulfolane has not been tested for chronic toxicity or carcinogenic activity, and BSC member Elaine Faustman, Ph.D., from the University of Washington, expressed a high level of support for going forward with further evaluation by NTP. Fellow concept reviewer Melissa McDiarmid, M.D., of the University of Maryland School of Medicine, agreed, noting, “This is precisely the situation that the NTP is supposed to serve.”

The HPV class of chemicals called phenolic benzotriazoles (PBZTs) was nominated to the NTP by NIEHS. Used as UV stabilizers within products to increase stability to light, there are 10 HPV PBZTs among the 29 compounds in the class, some of which are used in food contact polymers and adhesives, cosmetics, sunscreens, and fragrances. With high production and high potential for human exposure, the challenge will be to prioritize which of the chemicals to evaluate for potential health hazards, and which tests will eventually yield a class evaluation. BSC concept reviewers recommended that the NTP start its program on PBZTs with ADME (absorption, distribution, metabolism, excretion) and toxicokinetics tests to determine whether the active agent is a parent compound or a metabolite, and then move on with a testing funnel strategy similar to that used in the pharmaceutical industry for drug discovery.

The third proposed compound, trimethylsilyldiazomethane (TMSD), was nominated by the Occupational Safety and Health Administration (OSHA), due largely to the recent deaths of two chemists exposed to the agent in the laboratory workplace. TMSD is a synthetic methylating reagent used for organic synthesis and in analytical methods, such as gas chromatography. Originally developed as a less toxic and more stable substitute for the highly explosive compound diazomethane, there is currently very little toxicity data on TMSD, but dermal and inhalation exposures are likely in occupational settings. The BSC recommended moving forward with the proposed NTP testing program, but urged that extreme caution be exercised, including the use of appropriate personal protective equipment by testing personnel, due to the presumed acute toxicity of the compound.

### **Hair dye workshop supported**

The BSC favored a proposed workshop on permanent hair dyes. According to NTP presenter Ruth Lunn, Dr.P.H., the conference would advance the state of the science related to potential human health hazards associated with the widely used products, by focusing discussions on data gaps, research strategies, and testing methods. Potential carcinogenicity is a major concern, but studies to date have been unclear. Because there are so many different chemicals involved, and the dyes are all mixtures, determining safety of the products presents quite a challenge. Several BSC members noted that there are many scientific questions to be addressed, and the needed studies will be complex. Despite that



*Bucher presented his report about program events, highlights, and developments, and later returned to the podium to outline the Report on Carcinogens new review process. (Photos courtesy of Steve McCaw)*



*Nagarkatti gave a report on the NTP technical reports peer review. (Photo courtesy of Steve McCaw)*

cautionary note, the BSC supported moving forward with organizing the workshop. A representative from the Personal Care Products Council, in attendance, commended the NTP for tackling this issue, and said the industry looks forward to working with NTP to address this important subject.

The next BSC meeting is scheduled for June 21-22.

(Ernie Hood is a contract writer for the NIEHS Office of Communications and Public Liaison.)



*NIEHS/NTP toxicologist Chad Blystone, Ph.D., presented the research and testing concepts on sulfolane and PBZTs considered by the BSC. (Photo courtesy of Steve McCaw)*



*Kristina Thayer, Ph.D., director of the NTP Office of Health Assessment and Translation, briefed the BSC on the NTP Workshop on the Role of Environmental Chemicals in the Development of Diabetes and Obesity, held Jan. 11-13, 2011 in Raleigh, N.C. (Photo courtesy of Steve McCaw)*



*Eastmond kept the proceedings moving briskly, during the committee's daylong session. (Photo courtesy of Steve McCaw)*

## Proposed RoC review process

The BSC also spent time listening to comments from the public and receiving an update from the NTP on proposed changes on how the congressionally mandated Report on Carcinogens (RoC) would be developed.

The proposed changes to the RoC are intended to increase the transparency and openness of how the NTP reviews substances. Numerous opportunities for public input are built into the process.

NTP Associate Director John Bucher, Ph.D., walked the BSC through a number of changes that the NTP has made since the [original proposed review process](#) was released for public comment Oct. 31, 2011. Since then, the NTP has held a [public listening session](#), which brought 19 speakers, and a public comment period, allowing the NTP an opportunity to revise the process to accommodate some of the issues raised by the public.

As he thanked everyone for input, Bucher said all input has been considered and some revisions have been made. Bucher illustrated changes to the process, which is comprised of four parts: nomination and selection of candidate substances; scientific evaluation of candidate substances; public release of the draft RoC monograph and peer review; and HHS approval and release of the latest edition of the RoC.

BSC chair David Eastmond, Ph.D., from the University of California, Riverside, told the NTP, “The BSC supports what you are trying to do, and supports you going forward.”

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# Hundreds of rare genetic variants may cause a common autism phenotype

By Brant Hamel

Catalina Betancur, M.D., Ph.D., visited NIEHS Nov. 30 as a part of the Keystone Science Lecture Seminar Series. She delivered a presentation titled “Deconstructing ‘idiopathic’ autism: One behavioral syndrome, hundreds of genes,” which illustrated how rare defects in many different genes could give rise to a common phenotype diagnosed as autism. The presentation was hosted by Cindy Lawler, Ph.D., a scientific program administrator in the Division of Extramural Research and Training at NIEHS.

Betancur is an investigator for INSERM (the French National Institute of Health and Medical Research) at the Université Pierre et Marie Curie in Paris. Her research focuses on understanding the genetic underpinnings of autism with a focus on the heterogeneous mutations that give rise to common behavioral symptoms, possibly through gene-gene and gene-environment interactions.

## Autism is not a single disorder

Betancur explained that autism spectrum disorder is not a single disorder, but rather is a set of behavioral manifestations that may arise from any one of hundreds of individual genetic defects.

Although autistic patients have common behavioral symptoms, such as decreased social interaction, the etiology of the disease may be vastly different between patients. In the majority of the cases, the cause of autism is not known. Betancur has been able to pinpoint the rare genetic mutations that have given rise to about 20 percent of autistic cases and makes a persuasive argument that, with more screening and enhanced technologies, many more cases of idiopathic autism, or autism of unknown cause, would likely be diagnosed as resulting from diverse and rare genetic defects.

Betancur explained that autism is much like intellectual disability and epilepsy, which also result from a plethora of independent genetic mutations, yet produce a common phenotype. Interestingly, many of the genes known to be involved in autism are also linked to other disorders, such as intellectual disability, epilepsy, and schizophrenia. Betancur said that out of 91 X-linked genes associated with intellectual disability, 45 of them also were linked to autism. It is not yet clear why in some cases the same mutation may result in intellectual disability and in others autism, but it may depend on other genetic, environmental, or chance factors.

## Searching for rare variants to understand etiology of autism

Betancur described her work with the Paris Autism Research International SibpairStudy, which looked at 677 families with autism spectrum disorder from France and Sweden. With metabolic screening and a search for microdeletions and microduplications, her team was able to determine genetic causes for 20 percent of cases that had no previous molecular diagnosis. Most of the causes were extremely rare genetic defects that would not be commonly screened for.



*Betancur explained to audience members that hundreds of rare genetic defects can give rise to the common behavioral phenotype known as autism. She was one of several experts who participated in a two-day NIEHS-sponsored symposium on “Bioinformatics and Computational Approaches to Integrate Genes and Environment in Autism Research.” (Photo courtesy of Steve McCaw)*

As Betancur observed, one of the difficulties in showing that a genetic defect is involved in autism arises from the concepts of variable expressivity and incomplete penetrance. As an example of incomplete penetrance, Betancur pointed to cases of autism caused by DiGeorge syndrome, a deletion of a portion of chromosome 22 inherited from parents who do not have any signs of autism. In other cases variable expressivity occurs where the same genetic defect gives rise to different behavioral effects, as in the case of a family with mutations in neuroligin 4. One brother with the mutation had a severe case of autism, while the other brother with the identical mutation had a milder case of Asperger's syndrome.

Betancur concluded that more systematic molecular screening is necessary to diagnose the many rare genetic defects that contribute to the common behavioral manifestation known as autism. She argued that a paradigm shift was necessary, so that physicians and researchers would stop thinking about autism as a single disease with a common cause or set of common causes, but rather as a heterogeneous mix of many rare defects with variable clinical outcomes.



*Lecture host Lawler oversees the NIEHS portfolio of grants funding research into the environmental causes of autism. (Photo courtesy of Steve McCaw)*

## **New genes involved in autism**

Betancur's work has led to the discovery of new genes and signaling pathways involved in some cases of autism. Mutations in both neurexins, which reside on presynaptic neurons, and neuroligins, which reside on postsynaptic neurons and interact with neurexins, are linked to autism.

Betancur and her colleagues have been able to show that the intracellular protein SHANK3, downstream of this signaling pathway, is also involved in the etiology of autism. SHANK3 defects were found in three independent families including a 22q13 deletion in one family, also known as Phelan-McDermid syndrome; a frameshift mutation in another; and, interestingly, a third family where the son had a duplication of SHANK3 resulting in Asperger's, while the daughter had a deletion of SHANK3 resulting in autism.

Betancur estimated that SHANK3 might be involved in about 0.5 percent of global autism cases. She said that although that sounds like a small number, it would actually make it one of the most common causes of autism that can be traced to a specific genetic mutation.

(Brant Hamel, Ph.D., is a postdoctoral fellow in the NIEHS Molecular Endocrinology Group.)

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# NICEATM workshop report on vaccine testing now available

By Debbie McCarley and Cathy Sprankle

A workshop organized last year by the [NTP Interagency Center for the Evaluation of Alternative Toxicological Methods \(NICEATM\)](#) and the [Interagency Coordinating Committee on the Validation of Alternative Methods \(ICCVAM\)](#) is the subject of the current issue of the journal [Procedia in Vaccinology](#).

The [International Workshop on Alternative Methods to Reduce, Refine, and Replace the Use of Animals in Vaccine Potency and Safety Testing: State of the Science and Future Directions](#) was convened to review the state of the science of available alternative methods for human and veterinary vaccine potency and safety testing. Workshop participants also identified specific activities that will be needed to advance test methods with the potential to reduce, refine and replace animal use for vaccine testing.

## Identifying high priority vaccines for alternative testing

The workshop described in the current [Procedia in Vaccinology](#) was held Sept. 14-16, 2010, at NIH in Bethesda, Md. Nearly 200 scientists from 13 countries attended the workshop. Over 30 invited participants included scientists from U.S. government research and regulatory agencies as well as representatives from the governments of Japan, Canada, the United Kingdom, the Netherlands, and the European Union. National and multinational corporations and research institutions were also represented. The workshop report is comprised of 27 manuscripts and summarizes the plenary session speaker presentations as well as the conclusions and recommendations developed by the workshop participants.

“One of the key accomplishments of this workshop was the identification of the highest priority vaccines for future reduction, refinement, and replacement efforts,” noted Rear Adm. William Stokes, D.V.M., director of NICEATM. “Targeting specific vaccines will help focus research and validation efforts that can have a real impact on animal use and animal welfare.” He added that rabies vaccines were identified as one of the high priority vaccines. Reduction, refinement, and replacement of animal use for rabies vaccine potency testing was the subject of a recent [workshop](#) in October organized by NICEATM and ICCVAM.



*As acting chair of ICCVAM, Jodie Kulpa-Eddy, D.V.M., of the U.S. Department of Agriculture, welcomed participants to the workshop. (Photo courtesy of William Stokes)*



*In her keynote speech, Rear Adm. Anne Schuchat, M.D., director of the National Center for Immunization and Respiratory Diseases within the CDC, underscored the important role of safe and effective vaccinations in promoting public health. (Photo courtesy of William Stokes)*

## Recommending alternative methods

Vaccines improve animal and human health by preventing infectious diseases in people and animals. As a result of widespread human vaccination, smallpox has been globally eradicated, and many other diseases such as polio, measles, and rubella now occur only rarely in North America. Veterinary vaccines prevent a wide range of diseases in many animal populations, and contribute to human health by controlling diseases such as rabies that can be transmitted from animals to humans. However, testing necessary to ensure vaccine effectiveness and safety can involve large numbers of animals, and result in significant animal pain and distress. NICEATM and ICCVAM, whose mission is to promote alternative methods that can reduce, refine (enhance animal well-being, or lessen or avoid pain and distress), and replace animal use in testing, identified alternative test methods for vaccine potency and safety testing as one its highest priorities in a [five-year](#) plan issued in 2008.

In addition to prioritizing specific vaccines for future efforts, recommendations made by the participants of the September 2010 workshop included:

- Specific non-animal antigen quantification approaches that have successfully replaced animals for potency testing for some vaccines should be expanded for use with other vaccines through identification, purification, and characterization of vaccine protective antigens.
- Procedures should be implemented to reduce both the numbers of animals used and the pain and distress experienced by animals while and where animal testing is still needed.
- Efforts should be made to facilitate international harmonization and cooperation, as well as closer collaboration between human and veterinary vaccine researchers, as this will allow faster progress towards reduction, refinement, and replacement of animal use.

The workshop was organized by NICEATM and ICCVAM in partnership with the European Centre for the Validation of Alternative Methods, the Japanese Center for the Validation of Alternative Methods, and Health Canada. The workshop was co-sponsored by the Society of Toxicology.

(Debbie McCarley is the special assistant to Rear Adm. William Stokes, D.V.M., director of NICEATM. Cathy Sprankle is a communications specialist with ILS, Inc., support contractor for NICEATM.)

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## Workshop organizers

NICEATM and the ICCVAM Biologics Working Group (BWG) were primarily responsible for organizing the workshop. The BWG is co-chaired by Jodie Kulpa-Eddy, D.V.M., of the U.S. Department of Agriculture (USDA), and Richard McFarland, M.D., Ph.D., of the Center for Biologics Evaluation and Research at the U.S. Food and Drug Administration (FDA). Kulpa-Eddy is also currently chair of ICCVAM. In addition to FDA and USDA, the BWG includes scientists from the Centers for Disease Control and Prevention (CDC), U.S. Department of Defense, U.S. Department of the Interior, NIEHS, and the National Institute of Allergy and Infectious Diseases. Stokes and Warren Casey, Ph.D., deputy director of NICEATM, are the NIEHS representatives on the BWG.

Materials from the workshop, including the agenda, presentations from the workshop, and abstracts of posters presented at the workshop poster session, are available on the [NICEATM-ICCVAM website](#).

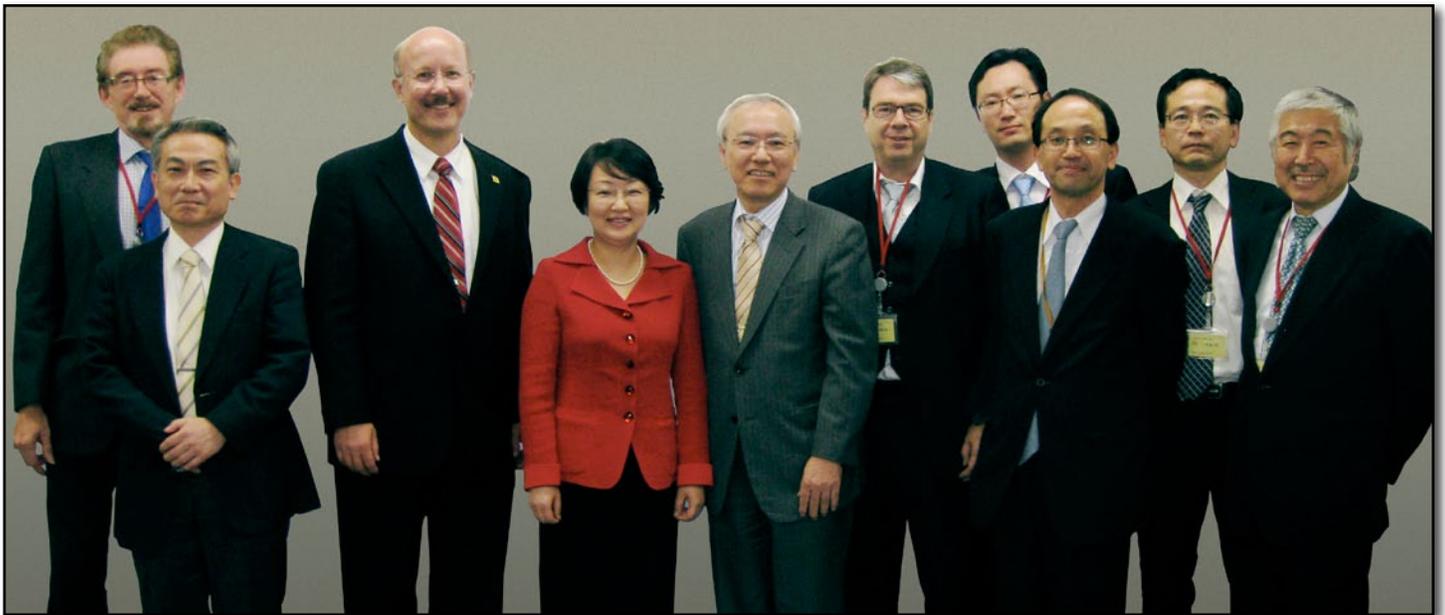
# Stokes builds international partnerships for advancing alternative testing

*By Debbie McCarley and Cathy Sprankle*

Rear Adm. William Stokes, D.V.M., director of the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), represented NIEHS and NICEATM at international scientific meetings in November. Stokes joined other scientists from around the world at meetings of the Japanese Society for Alternatives to Animal Experiments (JSAAE) and the advisory council of the Japanese Center for the Validation of Alternative Methods (JaCVAM). These meetings were part of a continuing effort to build global partnerships to advance alternatives to animal testing.

At the 24th annual meeting of the JSAAE Nov. 10–11 in Sendai, Japan, Stokes provided an update on recent progress and future planned activities of NICEATM and the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), which NICEATM administers. Stokes' presentation summarized NICEATM and ICCVAM contributions towards reducing, refining (enhancing animal welfare and eliminating or decreasing pain and distress), and replacing animal use for safety testing. The presentation also noted U.S. interagency efforts to accelerate development and use of more efficient safety testing approaches with the potential to better protect human health.

While at the JSAAE conference, Stokes attended a management team meeting for an ongoing study to evaluate a test method that uses human cells to identify substances with the potential to cause allergic contact dermatitis. Stokes and other meeting attendees received an update and provided feedback on current progress. Results of the study could support the use of this method to reduce or replace animal use. "Participation in validation studies to evaluate new test methods is an important aspect of our international interactions," Stokes commented. "Collaboration in the earlier stages of test method development greatly increases the chances that we'll later agree on recommendations on the appropriate uses of a new test method."



*Stokes joined participants at the Japanese advisory council meeting. Shown above, left to right, are Mike Inskip, senior biologist, Environmental Health, Science, and Research Bureau, Health Canada; Akiyoshi Nishikawa, M.D., Ph.D., director of Biological Safety Research Center, National Institute of Health Sciences, Japan; Stokes; Soon Young Han, Ph.D., director general of Toxicological Evaluation and Research Department, National Institute of Food and Drug Safety Evaluation, Korea; Yasuo Ohno, Ph.D., director general, National Institute of Health Sciences, Japan; Joachim Kreysa, head In Vitro Methods Unit, Joint Research Centre, Institute for Health and Consumer Protection, Italy; Kojima; Takuya Ikeda, Charles River Laboratories, Japan; and Tsutomu Kurosawa, Osaka University, Japan. (Photo courtesy of William Stokes)*

## **A cornerstone of NICEATM's international interactions**

Stokes also provided JSAAE attendees with an overview of the International Cooperation on Alternative Test Methods (ICATM). ICATM is an international partnership among national validation organizations that promote the advancement of refinement, reduction, and replacement alternatives for animal testing. The European Union, U.S., Japan, Canada, and South Korea are currently members of the cooperation agreement. The ICATM partners cooperate and collaborate on test method validation studies, peer review of new test methods, and development of harmonized recommendations for how new test methods can be used.

ICATM coordination meetings take place several times a year and provide an opportunity for the five ICATM organizations to discuss activities in the three major areas of cooperation. The meetings are planned to coincide with meetings of the Society of Toxicology and other gatherings of mutual interest to the participant organizations. "These regular interactions allow the ICATM partners to develop good communications and working relationships, which support our collaborations on test method development," noted Stokes.

## **Stokes participates in Japanese advisory council meeting**

Another important interaction activity for the ICATM partners is liaison membership on one another's advisory committees. Following the ICATM meeting, Stokes attended a meeting of the advisory council of JaCVAM, NICEATM's counterpart organization in Japan. The meeting took place at the Japanese Ministry of Health, Labour, and Welfare in Tokyo. The JaCVAM advisory council serves a similar role as the [Scientific Advisory Committee on Alternative Toxicological Methods \(SACATM\)](#). JaCVAM Director Hajime Kojima, Ph.D., attended the [SACATM meeting in June](#).

While attending the JaCVAM advisory council meeting, Stokes presented an update of NICEATM-ICCVAM and ICATM activities and an overview of U.S. initiatives to reduce, refine, and replace animal use in testing, including outcomes of the recent [NICEATM-ICCVAM workshop on alternative methods for rabies vaccine testing](#).

(Debbie McCarley is the special assistant to Rear Adm. William Stokes, D.V.M., director of NICEATM. Cathy Sprankle is a communications specialist with ILS, Inc., support contractor for NICEATM.)

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## **Casey presents at international meeting in Hungary**

*By Debbie McCarley and Cathy Sprankle*

Warren Casey, Ph.D., deputy director of the [National Toxicology Program \(NTP\) Interagency Center for the Evaluation of Alternative Toxicological Methods \(NICEATM\)](#), participated in an expert meeting in Budapest, Hungary, Nov. 30-Dec. 2, 2011. Casey discussed *in vitro* methods for identifying endocrine disruptors (EDs), substances that might interfere with normal hormone function.

Casey presented updates on NICEATM-ICCVAM ED-related activities at the Ninth Meeting of the Validation Management Group for Non-Animal Testing, sponsored by the [Organisation for Economic Co-operation and Development \(OECD\)](#).

Casey's presentations focused primarily on an *in vitro* method proposed for identifying EDs that interfere with normal estrogen function. This method, the BG1Luc estrogen receptor (ER) transcriptional activation (TA) test method, also known as the LUMI-CELL<sup>®</sup> ER assay, uses human ovarian cancer cells to identify substances that might act as ER agonists or antagonists, to stimulate or inhibit estrogenic activity.

## NICEATM-sponsored validation

NICEATM sponsored an international validation study of the BG1Luc ER TA test method in 2010, and convened an international independent scientific peer review panel to evaluate the study results earlier this year. The peer review was sponsored by the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), an interagency committee of the U.S. government administered by NICEATM.

ICCVAM final test method recommendations are provided in the ICCVAM Test Method Evaluation Report: The LUMI-CELL® ER (BG1Luc ER TA) Test Method: An In Vitro Assay for Identifying Human Estrogen Receptor Agonist and Antagonist Activity of Chemicals. These recommendations are the basis for a draft test guideline currently being considered for adoption by the OECD Test Guidelines Programme. If adopted next year, the BG1Luc ER TA test method could then be used internationally as a screening test to identify substances with ER agonist and antagonist activity.

The NICEATM–ICCVAM evaluation of the BG1Luc ER TA test method also supported the development of a performance-based test guideline being considered by OECD. Performance-based test guidelines provide standards by which test methods that assess a similar biological endpoint can be evaluated.

NICEATM and ICCVAM have a commitment to building global partnerships to advance alternatives to animal testing. Participation in events such as the recent OECD meeting is an important part of developing those partnerships.



*Casey, left, received his NIH Merit Award from NIEHS/ NTP Director Linda Birnbaum, Ph.D. (Photo courtesy of Steve McCaw)*

## Casey recognized for work on endocrine disruptors

At the NIEHS Awards Ceremony Dec. 6, Casey received a 2011 National Institutes of Health (NIH) Merit Award (see [related story](#)). The award was in recognition of his excellent performance in leading the international validation and interagency evaluation of new testing methods to support the federal government's endocrine disruptor chemical screening program.

Casey joined NIEHS in February 2010, after a number of years at GlaxoSmithKline and its predecessor companies, where he was a senior scientist in discovery and investigative toxicology. He is the author or co-author of 28 publications in peer-reviewed journals and holds three patents.

Casey received his undergraduate degree in biochemistry and his Ph.D. in microbiology from North Carolina State University (NCSU). Casey also serves as an adjunct associate professor in the NCSU Department of Microbiology and is a Diplomate of the American Board of Toxicology.

## Concerns about endocrine disruptors

EDs can interfere with the normal function of hormones in the endocrine system. Studies indicating that animal populations exposed to high levels of these substances have an increased incidence of reproductive and developmental abnormalities have raised concerns about the potential human health effects of these substances. While the impact of endocrine disruptors on human health remains poorly defined, these growing concerns have driven international interest in the availability of methods that can provide accurate and timely identification of potential endocrine disruptors.

The NICEATM-sponsored validation study of the BG1Luc ER TA test method included participating laboratories from the U.S., Europe, and Japan. Data from this study were reviewed at a March 2011 independent peer review [panel meeting](#) sponsored by ICCVAM. The peer review panel agreed with draft ICCVAM recommendations that the BG1Luc ER TA test method was appropriate for use as a screening test to identify substances with ER agonist and antagonist activity.

Final ICCVAM recommendations will be transmitted to federal agencies soon. The draft test guideline currently under consideration by OECD reflects the ICCVAM recommendations.

More information about the NICEATM-sponsored validation study and the ICCVAM evaluation of the BG1Luc ER TA test method is available on [the NICEATM-ICCVAM website](#).

(Debbie McCarley is the special assistant to Rear Adm. William Stokes, D.V.M., director of NICEATM. Cathy Sprankle is a communications specialist with ILS, Inc., support contractor for NICEATM.)

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## This month in EHP

*By Ian Thomas*

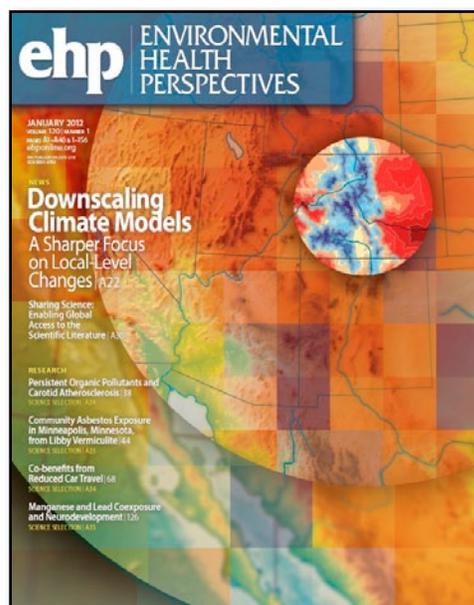
In its first lead story of 2012, the January issue of [Environmental Health Perspectives \(EHP\)](#) examines a new strategy for evaluating the impact of regional and local-level climate changes on public health. Downscaling climate models offers a clearer picture of how local climate may be affected in the future, by incorporating specific geographic details into a general circulation model.

In a second news story, titled “Trending Now: Using Social Media to Predict and Track Disease Outbreaks,” EHP explores how public health researchers are now using rapid information-exchange platforms, such as cell phones, social media, and other web-enabled applications, to predict and track outbreaks of infectious diseases.

This month’s [Researcher’s Perspective Podcast](#) features a discussion with NIEHS grantee [Robert Wright, M.D.](#), coauthor of a study on the neurodevelopmental effects of manganese and lead co-exposure appearing in this issue.



<http://twitter.com/ehponline>



Other research this month includes:

- Persistent Organic Pollutants and Carotid Atherosclerosis
- Community Asbestos Exposure in Minneapolis, Minnesota, from Libby Vermiculite
- Co-benefits from Reduced Car Travel

(Ian Thomas is a public affairs specialist with the NIEHS Office of Communications and Public Liaison, and a regular contributor to the Environmental Factor.)

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## NIEHS to hold minisymposia on epigenetics and BPA

*By Eddy Ball*

As part of its Keystone Science Lecture Seminar Series, NIEHS will present two minisymposia in January, organized by the NIEHS Division of Extramural Research and Training (DERT).

The first, exploring [Epigenetics, Chromatin Biology, Development, and Disease](#), will be held Jan. 10 from 8:00 a.m. to 5:00 p.m. in Rodbell Auditorium.

The event will feature talks by ten scientists, including researchers from the NIEHS intramural program, grantees, and other specialists in the field of epigenetics. The program will be moderated by DERT scientists Lisa Chadwick, Ph.D., Astrid Haugen, and Fred Tyson, Ph.D. A tentative agenda and list of speakers is posted [online](#).

[Registration](#) is free and open to the public.

The second will feature four NIEHS-grantees discussing their latest findings about bisphenol A (BPA) exposure and health. Hosted by NIEHS Health Scientist Administrator Jerry Heindel, Ph.D., the talks will take place Jan. 19 from 1:00 p.m. to 5:00 p.m. in Rodbell Auditorium. A tentative agenda and list of speakers is posted [online](#).

No registration is required for this event.

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## Society for Investigative Dermatology to meet May 9-12 in Raleigh

*By Eddy Ball*

The [Society for Investigative Dermatology \(SID\)](#) will hold its annual meeting at the Raleigh (N.C.) Convention Center May 9-12, assembling a diverse group of some 1,500 M.D. and Ph.D. scientists from around the globe to present and exchange findings on dermatology and skin biology.

The [meeting](#) is also a part of the society's celebration of its 75th anniversary as a professional organization, founded in 1937 to advance and promote the



sciences relevant to skin health and disease through education, advocacy, and scholarly exchange of scientific information. In addition to its [professional development meetings](#) and [annual retreats](#) for dermatology residents and Ph.D. students, SID publishes the Journal of Investigative Dermatology.

### Meeting details

SID offers discounted early [registrations](#) through March 16. The group will accept [abstract submissions](#) and applications for needs-based [Kligman Travel Fellowship Awards](#) by residents, trainees, students, or junior faculty through Jan. 12.

The meeting will feature five named and four state-of-the-art plenary lectures on topics ranging from stem cell regulation and genomic tracking of microbial pathogens to next gen sequencing and immune system regulation, along with a full schedule of concurrent minisymposia.

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## Extramural papers of the month

By [Nancy Lamontagne](#)

- [Rice consumption and arsenic exposure in pregnant women](#)
- [Consuming canned soup linked to higher BPA levels](#)
- [Dietary compounds could help protect kidney function](#)
- [Estrogen lessens effects of obesity and alcohol on breast cancer](#)



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

## Rice consumption and arsenic exposure in pregnant women

NIEHS grantees report that urinary arsenic concentrations were higher for pregnant women who had recently consumed rice than for those who had not. The findings highlight the need to monitor arsenic levels in food.

The researchers tested for arsenic in the urine of 229 pregnant women in New Hampshire, 73 of whom reported eating rice during the two days before urine collection. The arsenic concentration of the tap water in the women's homes was also tested to identify any exposure from drinking water. The women who reported eating rice during the two days prior to urine collection had a median total urinary arsenic concentration of 5.27 micrograms per liter, which was significantly different from the 3.38 micrograms per liter median concentration for those who did not consume rice.

The researchers note the need for more research to determine any health impacts of this source of exposure. Any identified health risks will also need to be weighed against the nutritional benefits of eating rice.

*Citation:* [Gilbert-Diamond D](#), [Cottingham KL](#), [Gruber JF](#), [Punshon T](#), [Sayarath V](#), [Gandolfi AJ](#), [Baker ER](#), [Jackson BP](#), [Folt CL](#), [Karagas MR](#). 2011. Rice consumption contributes to arsenic exposure in US women. *Proc Natl Acad Sci U S A* 108(51): 20656-20660.

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## Consuming canned soup linked to higher BPA levels

Researchers funded by NIEHS found that a group of volunteers who consumed a serving of canned soup every day for five days had more than a 1,000 percent increase in urinary bisphenol A (BPA) concentrations than when the same individuals consumed fresh soup daily for five days. The endocrine disruptor BPA is used in the lining of metal food and beverage cans and has been shown to have adverse health effects.

The researchers recruited 75 volunteers and asked a group of them to consume a 12-ounce serving of vegetarian canned soup each day for five days, while the rest consumed 12 ounces of vegetarian fresh soup, prepared without canned ingredients, daily for five days. After a two-day break, the groups reversed their assignments.

The researchers detected BPA in 77 percent of the urine samples taken after fresh soup consumption and in all of the samples after canned soup consumption. Eating a serving of canned soup daily was associated with a 1,221 percent increase in BPA concentration compared to levels in urine collected after consumption of fresh soup. Even though the elevation in urinary BPA concentrations might be temporary, the researchers comment that their findings could be important, especially as more and improved alternatives to epoxy linings are developed.

*Citation:* Carwile JL, Ye X, Zhou X, Calafat AM, Michels KB. 2011. Canned soup consumption and urinary bisphenol A: a randomized crossover trial. JAMA 306(20):2218-2220.

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## Dietary compounds could help protect kidney function

NIEHS-funded researchers have shown that compounds found in vegetables and cinnamon helped reduce kidney damage, and preserve kidney function in a mice model of diabetes. Medicines used to protect kidney function in people with diabetes often cause toxicity, so better therapies are needed.

The researchers experimented with sulforaphane, which is found in vegetables such as broccoli and cauliflower, as well as cinnamic aldehyde, a flavor component of cinnamon. These compounds activate a transcription factor called NFE-2-related factor 2 (Nrf2), which regulates expression of various genes to neutralize free radicals and accelerate toxin removal.

They induced diabetes in Nrf2 deficient (-/-) mice, as well as those that expressed Nrf2 (+/+), and then administered sulforaphane or cinnamic aldehyde two weeks later. In the mice expressing Nrf2, both compounds improved kidney performance, minimized kidney damage, and significantly lessened diabetes-associated symptoms, such as high blood sugar, excessive thirst, and weight loss. Since only the mice expressing Nrf2 showed beneficial effects, these results indicate that the compounds activate the Nrf2 pathway.

The researchers conclude that the study lays the foundation for clinical evaluation and future development of new Nrf2 activators that could prevent the onset and progression of kidney problems that are associated with diabetes.

*Citation:* Zheng H, Whitman SA, Wu W, Wondrak GT, Wong PK, Fang D, Zhang DD. 2011. Therapeutic potential of Nrf2 activators in streptozotocin-induced diabetic nephropathy. Diabetes 60(11):3055-3066.

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# Estrogen lessens effects of obesity and alcohol on breast cancer

Obesity and alcohol consumption increase risk for developing breast cancer and fatty liver, a condition where fat accumulates in liver cells. A study performed by NIEHS grantees has shown that estrogen can protect against these adverse health effects.

The researchers used female mice that mimic post menopause to study the effect of alcohol consumption, obesity, and estrogen supplementation on breast cancer. Overweight and obese mice consumed either water or alcohol, were implanted with placebo or estrogen pellets, and then injected with Met-1 breast cancer cells. The mice that consumed alcohol were more insulin sensitive and developed larger tumors than those that consumed water, and the obese mice developed tumors that were slightly larger than those in the overweight mice. However, all the mice receiving estrogen experienced loss of body fat, increased insulin sensitivity, suppressed tumor growth, reduced growth factors, and lessened retention of fat in the liver cells.

*Citation:* Hong J, Holcomb VB, Kushiro K, Núñez NP. 2011. Estrogen inhibits the effects of obesity and alcohol on mammary tumors and fatty liver. *Int J Oncol* 39(6):1443-1453.

(Nancy D. Lamontagne is a science writer with MDB, Inc., a contractor for the NIEHS Division of Extramural Research and Training, Superfund Research Program, and Worker Education and Training Program.)

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## Intramural papers of the month

*By Raluca Dumitru, Anshul Pandya, and Sonika Patial*

- [Caffeine strengthens connections between neurons in a little-known area of the brain](#)
- [Exposures to certain early-life factors may contribute to an early onset of uterine fibroids](#)
- [Snail and Slug activate TGF-beta in breast cancer](#)
- [Pregnane X receptor regulates liver metabolism](#)

## Caffeine strengthens connections between neurons in a little-known area of the brain

A recent study published by NIEHS scientists suggests how and where caffeine might act in the brain to increase cognitive function. Previous research shows that caffeine acts by blocking the inhibitory effects of adenosine on cyclic adenosine monophosphate (AMP) production in the brain. This study represents the first demonstration of long-lasting synaptic plasticity induced by in vivo exposure to caffeine, as reported in the journal *Nature Neuroscience*.

As a widely consumed stimulant, caffeine's effects on synaptic transmission in the CA2 area of the hippocampus, where adenosine A1 receptors are highly enriched, were not known. Rats were divided into three groups and given doses equivalent to two large cups of coffee, a highly caffeinated energy drink, or a dose that exceeded most people's daily consumption. All doses of caffeine strengthened the connections between neurons of CA2, but not in other areas of the hippocampus, a brain structure important for learning and memory.

These results provide a pleasingly simple explanation for the common daily human experience. Adenosine levels increase in the brain during the day, inhibiting the production of cyclic AMP. Although these effects recover during sleep, caffeine accelerates recovery by blocking any residual adenosine action and strengthens the activity of CA2 synapses of the hippocampus. This discovery also raises exciting new questions about the role of CA2 neurons in brain function.

*Citation:* [Simons SB](#), [Caruana DA](#), [Zhao M](#), [Dudek SM](#). 2011. Caffeine-induced synaptic potentiation in hippocampal CA2 neurons. *Nat Neurosci*; doi:10.1038/nn.2962 [Online 20 November 2011].

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## **Exposures to certain early-life factors may contribute to an early onset of uterine fibroids**

Researchers involved in the NIEHS Sister Study found associations between exposure to several early-life factors and the development of early-onset uterine fibroids in black women. These findings, which replicate many of the team's previously published associations among white women, add support to some hypotheses regarding the etiology of fibroids in women.

Uterine fibroids are highly prevalent benign tumors, with an estimated clinical prevalence as high as 50 percent for black women compared to 25 percent for white women. Blacks not only have an increased risk of developing fibroids, but also suffer more severe symptoms than whites.

The scientists examined early-life exposure to several factors in black women aged 35-59 years of age enrolled in the Sister Study cohort. The researchers found an elevated risk of early-onset uterine fibroids in association with *in utero* diethylstilbestrol (DES) exposure, *in utero* exposure to maternal diabetes or maternal hypertensive disorder, having been born preterm, having a monozygotic twin, being the firstborn child of a teenage mother, and consumption of soy formula.

Although the associations with multiple birth and maternal hypertensive disorder were not seen for white women, the general consistency of early-life findings for blacks and whites supports a possible role of early-life factors in fibroid development.

*Citation:* [D'Aloisio AA](#), [Baird DD](#), [DeRoo LA](#), [Sandler DP](#). 2011. Early-life exposures and early onset uterine leiomyomata in black women in the Sister Study. *Environ Health Perspect*; doi:10.1289/ehp.1103620 [Online 2 November 2011].

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## **Snail and Slug activate TGF-beta in breast cancer**

For the first time, scientists at NIEHS and SRA International, Inc. have determined the transcriptional consequences of exogenous expression of Snail and Slug in breast cancer. Snail and Slug are transcriptional repressors that have been proposed to mediate epithelial to mesenchymal transition, which has been implicated in tumor metastasis.

Researchers followed Snail and Slug expression by performing microarray analysis in a MCF-7 breast cancer cell line that did not express detectable levels of Snail and Slug. Adenovirus-infected cells served as the control. Microarray analysis showed that genes involved in the TGF-beta signaling pathway were upregulated, while genes responsible for a differentiated morphology were downregulated following Snail or Slug expression. Importantly, the overexpression of Snail and Slug changed the transcriptional signature from luminal to a more basal breast cancer that is commonly associated with highly invasive cancers.

This study suggests that the cell migration induced by Snail or Slug expression could be blocked by the addition of TGF-beta inhibitors, as inhibition of TGF-beta did not appear to affect the gene repression induced by Snail. However, the ability of cells to migrate was affected. Therefore, the sequential treatments with estrogenic agonists that control tumor growth and TGF-beta inhibitors to prevent cell migration may have therapeutic benefits.

*Citation:* [Dhasarathy A, Phadke D, Mav D, Shah RR, Wade PA](#). 2011. The transcription factors Snail and Slug activate the transforming growth factor-beta signaling pathway in breast cancer. *PLoS One* 6(10):e26514.

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## **Pregnane X receptor regulates liver metabolism**

NIEHS researchers have uncovered the mechanism for the repression of the estrogen sulfotransferase (SULT1E1) gene by rifampicin (RIF), an antibacterial and antifungal agent. This work makes the SULT1E1 gene the first gene that is repressed by pregnane X receptor (PXR) to be understood at the chromatin structure level. These findings have important public health implications as they suggest that PXR and constitutive active/androstane receptor (CAR) may cooperate in regulating hepatic levels of active estrogens, thereby affecting the physiology and pathophysiology of human liver.

The same group of NIEHS scientists previously published a study demonstrating that the activation of the SULT1E1 gene by xenobiotics is mediated by CAR, and that PXR activation by RIF repressed the SULT1E1 gene in human primary hepatocytes and hepatocellular carcinoma cells. The current study builds upon the earlier study.

Using chromatin immunoprecipitation and chromatin conformation capture assays, the research team identified the hepatocyte nuclear factor 4alpha (HNF4alpha) as the target of PXR to repress the SULT1E1 gene in human primary hepatocytes and hepatocellular carcinoma cells. In doing so, these investigators have determined how PXR cross-talks with HNF4alpha, disrupting an active chromatin structure and repressing the transcription of SULT1E1 gene. This PXR and CAR cooperation in regulating estrogen levels in the human liver may affect the physiology of the liver.

*Citation:* [Kodama S, Hosseinpour F, Goldstein JA, Negishi M](#). 2011. Liganded pregnane X receptor represses the human sulfotransferase SULT1E1 promoter through disrupting its chromatin structure. *Nucleic Acids Res* 39(19):8392-8403.

(Raluca Dumitru, M.D., Ph.D., is an Intramural Research Training Award (IRTA) fellow in the NIEHS Laboratory of Molecular Carcinogenesis Stem Cell Biology Group. Anshul Pandya, Ph.D., is an IRTA fellow in the Laboratory of Neurobiology Ion Channel Physiology Group. Sonika Patial, D.V.M., Ph.D., is a visiting fellow in the Laboratory of Signal Transduction Polypeptide Hormone Action Group.)

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# Inside the Institute

## Institute staff honored at 2011 NIEHS awards and international day

By Ian Thomas

NIEHS welcomed federal staff and contractors to Rodbell Auditorium Dec. 6 for its annual NIEHS Awards Ceremony and International Day festivities. As one of the biggest events of the year, the 2011 ceremony recognized individuals and groups for outstanding accomplishments, while also honoring NIEHS' rich cultural diversity with the annual International Day celebration afterwards.

"This ceremony spotlights the hard work and dedication of so many worthy people, and it's always such a pleasure to be a part of it," said [Nigel Walker, Ph.D.](#), NTP deputy director for science and the event's master of ceremonies.

### Merits of the highest honor

Among the most distinguished of awards presented at the ceremony were the 25 NIH Merit Awards, honors given on behalf of the NIEHS director in recognition of outstanding contributions toward leadership, scientific research, and scientific and administrative management.

"Winning a Merit Award is a testament to the dedication and innovation of everyone involved with NIEHS' ethics program," said [David Resnik, J.D., Ph.D.](#), a bioethicist who, along with his team from the NIEHS Ethics Office, garnered a compliance score of 100 percent for its ethics and research conduct training programs. "But beyond that, it also signifies this Institute's commitment to maintaining strong ethical standards, and I'm exceptionally proud to be part of it."

Other awards presented were the NIEHS Unsung Hero Awards, recognizing employees who make valuable contributions that have a huge impact on the programs of the Institute, and the NIEHS Peer Awards, honors nominated by colleagues that honor employees who have consistently provided extraordinary assistance to their fellow workers.

"I really can't tell you what a wonderful honor it is to win this award," said [Amy Johnson](#), an Unsung Hero Award winner and a member of NIEHS since 1978. "Scientists are an incredible breed of people, and I feel so very fortunate to have worked alongside some of the best during my time here."

The ceremony also recognized winners of the Green Champions Awards, Fellows Awards for Research Excellence (FARE), and NIH Director's Awards, all presented earlier in the year.



*Walker was an engaging host who moved the ceremony along with his good-natured anecdotes about colleagues, including Birnbaum, that kept the audience laughing and attentive. (Photo courtesy of Steve McCaw)*



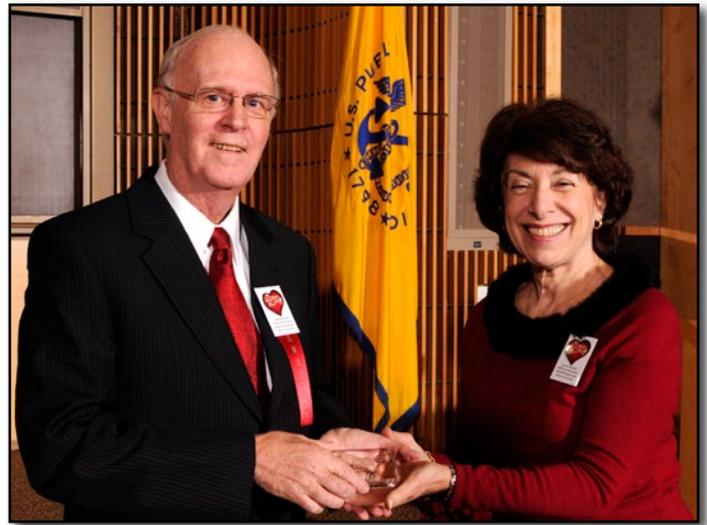
*Although Walker commanded the podium during most of the ceremony, Birnbaum had the last word, as she thanked all of the employees at NIEHS for their contributions to the Institute's mission. (Photo courtesy of Steve McCaw)*

## Proud reflection

NIEHS had no shortage of achievement in 2011. Be it the Institute's field-leading work with the GuLF STUDY, a health study of oil spill cleanup workers, or its highly publicized release of the 12th Report on Carcinogens, the Institute and its personnel continue to raise the bar as they move forward into 2012 and beyond.

"Our sincerest congratulations go out to everyone here at NIEHS, for a phenomenal job in 2011," said NIEHS/NTP Director Linda Birnbaum, Ph.D. "Regardless of whether you won an award today, you all deserve one, which is why I consider it such an honor to be your director."

There is a [complete list](#) available of all 2011 Merit, Unsung Hero, Peer, Special Appreciation, and Honorable Mention awardees.



*Leading off the ceremony was the presentation of the first of two Unsung Hero Awards to NTP Technical Writer/Editor Charles Alden, Ph.D., for maintaining the high standards expected of the NTP Technical Report Series. (Photo courtesy of Steve McCaw)*

## A collage of culture

Following the awards ceremony, attendees were invited to the cafeteria for an afternoon of food, music, and educational displays, compliments of the 2011 International Day. Highlighted by its elaborate menu, featuring an array of Indian, Latin American, Asian-Pacific, and Native American dishes among others, the celebration treated visitors to a multicultural spectrum of entertainment, including a fashion show of international holiday attire, traditional Christmas tree decorating, and Native American storytelling.

"International Day is one day of the year when we recognize all of the cultures that are represented across NIEHS," said [Brad Collins](#), a chemist and program officer with NTP who chairs the NIEHS Diversity Council. "People come from all over the world to work here. Because of that, Institute employees can experience a fantastic variety of different cultures and, more times than not, they need only look to the next lab or cubical to do it."



*The ceremony concluded with the recognition of recipients of earlier awards, such as trainees who were FARE winners. (Photo courtesy of Steve McCaw)*



The food was tasty, plentiful, and varied. Shown above, left to right, postdoctoral fellows Raj Gosavi, Ph.D., and Sindura Ganapathi, Ph.D., prepared for a hearty afternoon snack. (Photo courtesy of Steve McCaw)



International Day is always a memorable time for the children of NIEHS employees. They can come with their parents or participate as a part of the First Environments Daycare program located on the adjacent EPA campus. (Photo courtesy of Steve McCaw)



In a joyous burst of enthusiasm, Dona McNeill, left, joined Bono Sen, Ph.D., dressed in traditional Indian attire, in a spontaneous dance. (Photo courtesy of Steve McCaw)



The band Saludos Compay played a range of Latin music for listening and dancing. (Photo courtesy of Steve McCaw)

(Ian Thomas is a public affairs specialist with the NIEHS Office of Communications and Public Liaison, and a regular contributor to the Environmental Factor.)

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# CFC enjoys another record year

By Eddy Ball

NIEHS wrapped-up its annual event-packed Combined Federal Campaign (CFC) Dec. 15, 2011, setting yet another record by raising \$110,000 in pledges from more than 200 employees. The 2011 campaign surpassed its own goal of \$105,000 and last year's record of \$107,000.

In an announcement to employees, NIEHS/NTP Director Linda Birnbaum, Ph.D., offered those who made the record possible her sincere thanks. "I am so proud of you for helping not only our community, but also those in need," she said. "Your voluntary giving is so much appreciated in times when our economy is suffering."

Birnbaum also recognized the exceptional performance of CFC co-chairs Ron Cannon and Cindy Innes, as well as division chairs and co-chairs. True to her message throughout the campaign, Birnbaum, who supported the effort with frequent emails to employees, had a final word for NIEHS employees.

"I would like to remind you, as the 2011 NIEHS CFC campaign activities are winding down, that last minute voluntary donation can still be accepted," she said.



CFC co-chair Cindy Innes  
(Photo courtesy of Steve McCaw)



CFC co-chair Ron Cannon  
(Photo courtesy of Steve McCaw)

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## Division chairs and co-chairs

### Extramural Research and Training

Elizabeth Ruben (Chair)  
Danielle Carlin  
Barb Gittleman

### Intramural Research

Bob Petrovich (Chair)  
David Armstrong  
Terry Blankenship-Paris  
Shannon Duncan  
Gina Goulding  
Gezell Jones  
Pat Johnson

### NTP

Rachel Frawley (Keystone Chair)  
Eli Ney  
Denise Lasko  
Veronica Robinson  
Cynthia Rider  
Diane Spencer  
Pat Stockton  
Sheila Withers

### Office of Director

Debbie Wales (Chair)  
Judy Hanson

### Office of Human Resources

Fran Cowens

### Office of Management

Dona McNeill (Chair)  
Pat Barbour  
Lindia Ingram  
Jenn Evans  
Jim McDonough  
Dudley Riner  
Tameka Thomas

### Office of Research Facilities

Paul Poliachik

# NTA celebrates grand opening of resource room

By Ed Kang

With a ceremonial coffee hour and open house Nov. 30, the NIEHS Trainees Assembly (NTA) proudly opened the doors to a new resource room that is specifically designed to accommodate the interests of the Institute's 220-plus postdoctoral students and fellows. The grand opening was reason for celebration, as the NTA has long wanted a space that would perform triple duty as a resource room, a meeting space for committee meetings, and a private location for postdocs to rehearse and conduct interviews.

NIEHS research fellows have big plans for the modest-sized room that will support the goals of the NTA to organize and promote educational activities, including training courses and seminars. "It's been a long time coming," said former NTA Steering Committee co-chair Nisha Cavanaugh, Ph.D., a postdoctoral fellow in the DNA Repair and Nucleic Acid Enzymology Group. "This will be a convenient and central place for steering committee and subcommittee meetings."

## A central nexus for trainees

This sentiment was echoed by Sarah Swerdlow, Ph.D., a postdoctoral trainee in the Mechanisms of Mutation Group. "This is going to be very good for us. We're in labs spread out across the Institute, so to have one place, just for us, is going to really enhance the postdoc experience."

"We also have lots of stuff," added Jill Hesse, Ph.D., referring to years of archived meeting notes, as well as current resources, contacts, and brochures. Hesse, who works in the Environmental Stress and Cancer Group, pointed to the benefits of having a common place for all these resources. "Now postdocs know right where to go for all their needs," she said.

One example of the resource room's benefit was provided by the NTA Steering Committee on the recent NIEHS Science Awards Day poster judging. "It was really important for the postdocs to see the feedback provided by the judging panel," Cavanaugh commented. "The resource room provided an easy-to-access, central repository for those scoring sheets, so anyone, anytime could come and review their feedback."



Warm beverages, snacks, and, of course, fellowship mark the opening of the NTA resource room, which is now officially open for business. Shown, left to right, are postdoctoral fellows Tracy Clement, Ph.D., Hesse, Cavanaugh, Tammy Collins, Ph.D., and Ashley Godfrey, Ph.D. (Photo courtesy of Steve McCaw)



Various brochures, training materials, and applications will now have a full-time home. Formerly, these resources were housed in different offices throughout the Institute. Shown, left to right are Clement, Godfrey, and postdoctoral fellow Vijayakanth Pagadala, Ph.D. (Photo courtesy of Steve McCaw)

The new room also helps to fulfill another NTA goal of assisting postdocs in identifying and seeking future employment opportunities in both traditional and non-traditional career paths. Hesse noted that the privacy of the new space will be conducive for practicing or doing actual interviews, either in person or by phone. “It’s not practical to have these types of conversations at the bench or in a shared workspace.”

Hesse and others enthusiastically added, “We love Dr. Miller!” referring to David Miller, Ph.D., chief of the Laboratory of Toxicology and Pharmacology and former acting NIEHS scientific director. Miller’s ongoing support of the postdoc community and the efforts of the NTA enabled the use of the space, and provided the necessary furniture, phones, and data connectivity.

The NTA resource room is located in the F module of Building 101 in room F182.

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



*The NTA-hosted coffee hour drew thirsty and curious postdocs to enjoy the new space for the first time. (Photo courtesy of Steve McCaw)*

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**NIEHS**  
National Institute of  
Environmental Health Sciences

*NIH...Turning Discovery Into Health*

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