

January 2011

NIEHS Spotlight



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[Tice talks Tox21](#)

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[Birnbaum addresses Mt. Sinai autism workshop](#)

NIEHS/NTP Director Linda Birnbaum, Ph.D., was the keynote speaker at a scientific workshop at the New York Academy of Medicine Dec. 8.

Science Notebook



[Birnbaum presents Whittenberger Symposium keynote lecture](#)

NIEHS/NTP Director Linda Birnbaum, Ph.D., added yet another laurel to her long list of honors with her keynote talk at the 13th James L. Whittenberger Symposium Dec. 17.



[Aston-Jones explores the biology of addiction](#)

Neurobiologist Gary Aston-Jones, Ph.D., discussed the role of orexin neurons in reward-seeking behavior and addiction during his Distinguished Lecture Nov. 23.



[Novel small RNA molecules regulate stem cell self-renewal](#)

Yale University School of Medicine researcher Haifan Lin, Ph.D., visited NIEHS recently to talk about exciting new discoveries he has made with stem cells.



[Guest lecture underscores environmental links to autism](#)

Environmental factors are likely among several contributors to the rapid rise in new cases of autism, according to guest lecturer Irva Hertz-Picciotto, Ph.D.



[Crouch links RNase H to infectious and genetic diseases](#)

A presentation by guest lecturer Robert Crouch, Ph.D. provided insight into an RNA cleaving enzyme, whose production he playfully called "the purpose in life."

NIEHS Spotlight



[Balbus reports on US federal climate change and health initiatives](#) Video

NIEHS Senior Advisor for Public Health John Balbus, M.D., highlighted new collaborative efforts to address climate change and public health.



[NIEHS holds public partners meeting](#)

The annual NIEHS Public Interest Partners Meeting Dec. 9 in Washington, D.C., featured open discussions with NIEHS/NTP Director Linda Birnbaum, Ph.D.



[Clinical Research Unit enhances intramural research](#)

In December, the CRU enrolled its 500th study participant and experienced its busiest week to date, with 42 people volunteering to take part in a clinical study.



[NIEHS completes draft of metrics manual](#)

Now available for public review, the new PEPH Evaluation Metrics Manual is designed to help grantees identify and measure their partnership work.



[Oil spill update – NIEHS activities in the Gulf](#)

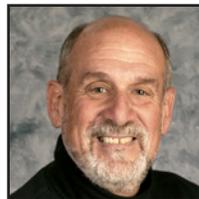
The Gulf oil spill may be largely out of the headlines these days, but NIEHS continues its efforts to better understand its impact on the health of the people of the region.



[NIEHS scientists join tour of Morehead Planetarium](#)

NIEHS women scientists joined their colleagues for a special behind-the-scenes tour of the Morehead Planetarium at UNC-CH on Nov. 17.

Science Notebook



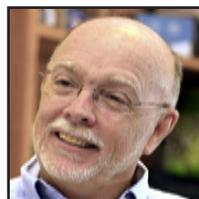
[Study proposes new paradigm for the field of environmental toxicology](#)

A new NIEHS-funded paper offers insight into how organic pollutants impact the delivery of therapeutic drugs to the central nervous system.



[Chatterjee wins Young Investigator Award](#)

Visiting Fellow Saurabh Chatterjee, Ph.D., was recognized at the Annual Meeting of the Society for Free Radical Biology and Medicine.



[Highlighting the role of nutrition in host susceptibility](#)

The old adage about an apple a day keeping the doctor away picked up a Superfund twist during a half-day workshop Dec. 2 at the University of Kentucky.



[Miller presents study on erionite exposure and mesothelioma](#)

A collaborative effort in the U.S., including work by NIEHS Senior Medical Adviser Aubrey Miller, M.D., may be able to reduce exposure to a cancer-causing mineral.



[Review emphasizes potential dangers of e-waste](#) Video

A new NIEHS-funded analysis is sending a wake-up call on the emerging health concerns posed by electronic waste disposal practices worldwide.

NIEHS Spotlight



[Hughes represents NIEHS at White House forum](#)

WETP Director Chip Hughes joined top-level policy and practice leaders Dec. 15 in Washington, D.C. for an historic collaboration on environmental justice issues.



[NIEHS helps launch Healthy People 2020](#)

The HHS Healthy People initiative looks to its third decade of striving for a society in which all people live longer, healthier lives.



[Philbert named dean at Michigan](#)

The University of Michigan announced the appointment of NIEHS grantee and former council member Martin Philbert, Ph.D., as dean of the School of Public Health.

Inside the Institute



[NIEHS holds annual awards ceremony](#)

NIEHS recognized employees' accomplishments at the 2010 NIEHS Awards Ceremony in Rodbell Auditorium Dec. 16, followed by the annual International Day celebration.



[CFC has best year yet](#)

2010 was a banner year for NIEHS participation in the Combined Federal Campaign, with a record total of \$106,000 pledged.

Science Notebook



[Study finds mitochondrial dysfunction in autistic children](#)

A new exploratory study funded in part by NIEHS finds that deficits in the ability to produce cellular energy are significantly more common in children with autism.



[NIEHS to fund new mitochondrial dysfunction studies](#)

A new funding opportunity announcement calls for projects to identify biomarkers for early detection of environmentally induced mitochondrial dysfunction.



[Casey presents at international meeting on alternatives for endocrine disruptors](#)

NTP scientist Warren Casey, Ph.D., participated in an expert meeting to discuss *in vitro* methods for detecting substances that might interfere with normal hormone function.



[New green safety testing methods available to identify ACD](#)

NIEHS has endorsed two new alternative safety-testing methods to determine if chemicals and products may cause allergic skin reactions.



[Stokes presents at international meeting on alternatives for vaccine testing](#)

NTP scientist William Stokes, D.V.M., traveled to Germany to share recommendations for reducing, refining, and eventually replacing animal use for testing vaccines.

2010 papers of the year

Of the more than 2,900 papers published by NIEHS-supported researchers in 2010, 21 publications were chosen as Papers of the Year.

- [Prenatal exposure to phthalates is associated with reduced masculine behavior in boys](#)
- [Obesity is a tumor promoter](#)
- [Fetal and early life exposures to BPA may increase the risk of cancer](#)
- [Mother's exposure to urban air pollutants affects children's cognitive abilities](#)
- [Researchers map the first human epigenome](#)
- [Living, breathing lung-on-a-chip](#)
- [Flame retardants linked to reduced human fertility](#)
- [Arsenic-related mortality in Bangladesh](#)
- [Genetic studies identify DNA sequences associated with lung function](#)
- [Acetaminophen-induced transcriptional changes predict liver injury](#)
- [Early-life exposures are linked to development of uterine fibroids](#)
- [Stem cell survival advantage toward arsenic drives malignant transformation](#)
- [Cholesterol trafficking linked to inflammatory response](#)
- [Genome instability due to ribonucleotide incorporation into DNA](#)
- [Gender differences in glucocorticoid-mediated inflammation](#)
- [Paused Pol II regulates gene activity](#)
- [Effects of low dose atrazine on pubertal timing and prostate development of male rats](#)
- [Genetic and epigenetic mechanisms in liver tumors of oxazepam-exposed mice](#)
- [Useful immunohistochemical markers of tumor differentiation](#)
- [Arsenic, stem cells and the developmental basis of adult cancer](#)
- [Cancer in experimental animals exposed to arsenic and arsenic compounds](#)

Science Notebook



[This month in EHP](#)

With a vivid cover photo of a melting iceberg, the January issue of Environmental Health Perspectives revisits climate change.



[Susan Amara to present distinguished lecture](#)

The NIEHS 2010-2011 Distinguished Lecture Series returns to the fascinating world of neuroscience with its next talk Jan. 11 by neurobiologist Susan Amara, Ph.D.

Extramural Research

[Extramural papers of the month](#)

- [BPA exposure and oocyte quality](#)
- [Freeway proximity and autism](#)
- [A simple sensor for explosive chemicals](#)
- [Blood DNA methylation related to heart disease and stroke](#)

Intramural Research

[Intramural papers of the month](#)

- [Paused Pol II regulates gene activity](#)
- [Estrogen receptor alpha has cell specific roles in the endometrium](#)
- [Involvement of human CYP epoxygenases in hypertension and kidney damage](#)
- [DNA polymerase delta replicates on lagging strand](#)

Calendar of Upcoming Events

- **Jan. 4 (Offsite Event)** in 103 Bryan Research Building on the campus of Duke University — Ion Channel Seminar Series with David Armstrong, Ph.D., presenting “Phosphorylopathies: Losing Control of Ion Channel Phosphorylation”
- **Jan. 10** in Rodbell Auditorium, 12:00-1:30 p.m. — Partnerships for Environmental Public Health - Measuring Partnership Activities: Release of the Evaluation Metrics Manual
- **Jan. 11** in Rodbell Auditorium, 11:00 a.m.-12:00 p.m. — Distinguished Lecture with Susan Amara, Ph.D., speaking on “The Ins and Outs of Neurotransmitter Transporters”
- **Jan. 11-13 (Offsite Event)** at the Raleigh Marriott Crabtree Valley — NTP Workshop: Role of Environmental Chemicals in the Development of Diabetes and Obesity
- **Jan. 13** in Rall D450, 10:00-11:00 a.m. — Laboratory of Molecular Carcinogenesis Seminar Series with Sharon Dent, Ph.D., presenting “The Secret Lives of Histone Modifying Enzymes”
- **Jan. 19** in Rodbell Auditorium, 10:00 a.m.-12:00 p.m. — Martin Luther King Jr. Day Observance featuring a presentation by North Carolina Rep. Mickey Michaux
- **Jan. 24** in Rodbell Auditorium, 11:00 a.m.-12:00 p.m. — Laboratory of Molecular Genetics Fellows Invited Guest Lecture with Yikang Rong, Ph.D., topic TBA
- **Jan. 25** [online](#), 1:00-2:00 p.m. — Partnerships for Environmental Public Health - Overview of the Evaluation Metrics Manual ([register](#))
- **Jan. 26** in Rodbell Auditorium, 8:30 a.m.-5:00 p.m. — NTP Technical Reports and Special Emphasis Panels Meeting
- **Feb. 1** in Rodbell Auditorium, 8:00 a.m.-12:00 p.m. —NIEHS Centers for Disease Investigation through Specialized Clinically-Oriented Ventures in Environmental Research (DISCOVER) Conference: Presentations on Research Approach and Early Findings
- **Feb. 1 (Offsite Event)** in Room 147, Nanaline Duke Building on the campus of Duke University, 12:30-1:30 p.m. — Tuesday Seminar Series with Mike Resnick, Ph.D., topic TBA
- View More Events: [NIEHS Public Calendar](#)

NIEHS Spotlight

Woychik named NIEHS deputy director

By Eddy Ball

In a message to employees Dec. 2, NIEHS/NTP Director Linda Birnbaum, Ph.D., announced the appointment of Richard Woychik, Ph.D., as the Institute's deputy director. Woychik, who officially begins work Jan. 30, leaves his current position as president and chief executive officer of [The Jackson Laboratory](#), headquartered in Bar Harbor, Maine with more than 1400 employees.

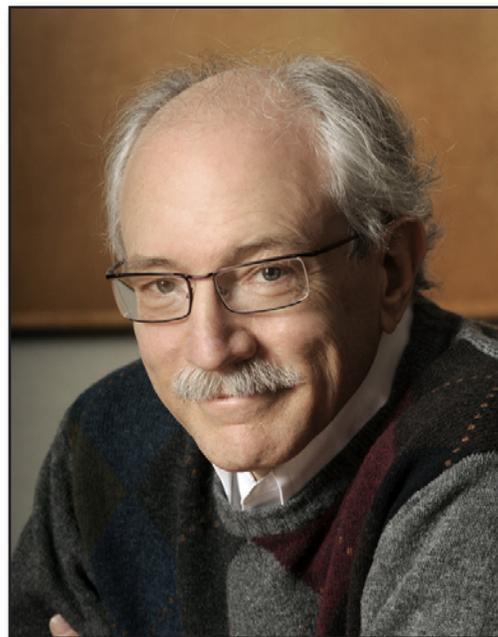
In her announcement, Birnbaum wrote, "Dr. Woychik brings a wealth of scientific expertise and administrative experience to the role of deputy director of the NIEHS, [and] I have every confidence in his ability to do an extraordinary job in this critical role at the Institute."

For his part, Woychik says he envisions the next phase of his professional life as an opportunity to help set the stage for the environmental sciences community in the post-genome era, the topic of his July 14 interview presentation at NIEHS. "The original genome sequencing," he explains, "while hugely challenging in its own right, was just the first step in understanding human biology and disease. The much more difficult next steps involve unraveling the interaction of genetic and environmental factors in human health in order to prevent and treat disease, and optimize quality of life worldwide."

Birnbaum explained that Woychik's initial efforts will focus on leading the development of a strategic plan for the Institute covering the years 2012 through 2017 — a roadmap for NIEHS initiatives in preventive public health that range from basic research and community-based participatory research to a growing involvement in global health. The deputy director has high-level responsibilities in planning and policy. Woychik will also serve as a prominent spokesperson for the Institute and its mission.

A leading mammalian geneticist with more than 80 publications and many honors to his credit, Woychik completed his B.S. and M.S. at the University of Wisconsin-Madison, and earned his Ph.D. in molecular biology at Case Western Reserve University. He completed his postdoctoral training in the laboratory of [Philip Leder, M.D.](#), at Harvard Medical School with fellowship support from the Jane Coffin Childs Memorial Fund for Medical Research and from the Howard Hughes Medical Institute.

Woychik has a wide range of scientific and leadership experience in academic, government, and private sector positions that will serve him well in his new role at NIEHS. In addition to his work at The Jackson Laboratory, he served as scientific officer for Lynx Therapeutics; head of the Parke-Davis Laboratory of Molecular Genetics; professor within the Departments of Pediatrics, Genetics and Pharmacology at the Case Western Reserve University; and worked his way up through the ranks over the course of 10 years to become the head of the Mammalian Genetics Section in the Biology Division, and then director of the Office of Functional Genomics at the Oak Ridge National Laboratory.



In the scientific world, Woychik has achieved renown for using molecular genetics to identify and study genes involved in a variety of human disorders. (Photo courtesy of Steve McCaw)

During Woychik’s nine-year tenure at The Jackson Laboratory, the institution grew significantly. The total operating budget almost doubled from \$103.8 million in 2002 to \$200.1 million in 2010. The Laboratory completed construction and renovation projects totaling \$80 million. And the Laboratory’s JAX-West facility in California moved into larger facilities in Sacramento and expanded to more than 100 employees.

His laboratory was the first to clone the agouti gene and to decipher its role in the development of obesity and type 2 diabetes. Additionally, his group went on to identify the first gene associated with polycystic kidney disease and to implicate the protocadherin family in the development of age-related hearing loss. During his time at Lynx Therapeutics, he worked on advancing the early technologies for enabling the Massively Parallel Signature Sequencing (MPSS) next-generation approach for high throughput genome analyses. His current research interests involve using whole genome approaches to better understand how genetics, epigenetics, and, most importantly, the environment impact human health.

Woychik’s appointment is another milestone in Birnbaum’s quest to build her new leadership team at NIEHS. Searches are currently under way for the Institute’s scientific director and clinical director.

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Collman named extramural director

By Thaddeus Schug

NIEHS/NTP Director Linda Birnbaum, Ph.D., reached another milestone in her quest to build a quality leadership team with the appointment of longtime NIEHS epidemiologist and scientific program administrator Gwen Collman, Ph.D., as director of the Division of Extramural Research and Training (DERT). The selection of Collman, who served for the past two years as acting director, was announced Dec. 2 in a message from Birnbaum to employees of NIEHS and NTP.



Collman leads a division that is organized into seven branches and centers, composed of 60 full-time federal employees. Each year, the extramural program is responsible for awarding approximately 874 research grants for a total of approximately \$388 million. (Photo courtesy of Amy Collman)

Linked video:
[Collman describes the power of the NIEHS extramural program \(3:06\)](#)
(Launches in new window)

Download Media Player: [Quicktime](#)

“I am pleased to appoint Gwen to a full-time seat on our leadership team,” wrote Birnbaum. “Gwen has done a tremendous job advancing the Institute’s research priorities during her tenure as interim director of DERT. Her leadership skills were critical to implementation of NIEHS’ portion of the American Recovery and Reinvestment Act (ARRA), while also guiding management and review of over 1000 grants per year.”

Collman plans to draw on her vast scientific and leadership experience to build on the many successful extramural programs initiated during her tenure and to work with NIEHS leadership to strategically identify new directions and opportunities in environmental health science. “The challenge for the NIEHS extramural

division is to continue to work effectively with our grantees, business partners, community members, and federal partners so that we are funding the most meaningful science,” said Collman.

“We have a very talented and committed team of scientists, grants management experts, program evaluators, and support staff in DERT, and I am excited to work with them to meet the challenges of the future,” said Collman. “It is important for our division to anticipate scientific opportunities and challenges, to build strong relationships with scientists, and to provide comprehensive information on our research priorities and the procedures to obtain funding for our many stakeholders.”

A productive 26-year career at NIEHS

Collman joined NIEHS as an epidemiologist in the Institute’s Epidemiology Branch, following completion of her doctorate in environmental epidemiology at the University of North Carolina at Chapel Hill (UNC-CH) School of Public Health in 1984. In 1992, she moved to DERT as a scientific program administrator charged with building a strong portfolio in epidemiology.

In 2003, Collman became chief of the DERT Susceptibility and Population Health Branch, a post she held until being named acting director of the division in 2008. She has been recognized many times for her work and has to her credit an impressive list of NIH Merit and Director Awards and other honors, scientific and policy publications, and presentations to a wide variety of audiences. She is recognized internationally for her work creating opportunities in public health, especially in environmental epidemiology, and has served as a councilor for the International Society of Environmental Epidemiology.

In addition to building a grant portfolio in environmental and molecular epidemiology, Collman developed and managed several complex multidisciplinary research programs that include involvement of communities in partnerships with researchers. These include the NIEHS Breast Cancer and the Environment Research Centers Program and the NIEHS/EPA Centers for Children’s Environmental Health and Disease Prevention and the Genes, Environment and Health Initiative.

Collman, is a longtime advocate of environmental justice and community-based participatory research. Under her leadership, DERT is entering the first phase of its new Partnerships for Environmental Public Health initiative — an umbrella program for advancing the impact of environmental public health research at local, regional, and national levels.

Looking toward the future

Earlier this year, Collman was honored by her alma mater with the 2009 H.A. Tyroler Distinguished Alumni Award, presented by the UNC-CH Epidemiology Chapter of the General Alumni Association ([see story](#)). Her talk focused on a theme she has emphasized during her career at NIEHS and one that will continue to play a critical role in the future, community engagement in environmental epidemiology.

During her interview lecture Aug. 16 at NIEHS, Collman expanded on yet another theme that will surely mark her leadership of DERT, “The Power of the NIEHS Extramural Program.” In her presentation, Collman pointed to the program’s extensive grantee base, its impact on the direction of scientific research, and its network of partners worldwide as tools for influencing the future of public health domestically and globally.

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

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NTP board reviews Biomolecular Screening Branch and Tox21

By Ernie Hood

Predictive toxicology – the emerging science that uses high-throughput screening of chemicals in cells and cell lines to understand outcomes in human health and disease – was the focus of the [NTP Board of Scientific Counselors \(BSC\)](#) meeting Nov. 30-Dec. 1 at NIEHS. Much of the meeting was taken up by the board’s review of the Biomolecular Screening Branch (BSB), which is responsible for NIEHS/NTP participation in Tox21, the multi-agency, multidisciplinary collaboration designed to initiate a new era in toxicity testing for the 21st century.

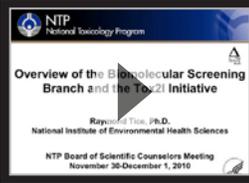
The first BSC review of the BSB and Tox21 comes at a propitious moment. “This is the first time that the BSC has had an opportunity to consider and comment on the breadth of our activities and our plans for the future,” said Raymond Tice, Ph.D., chief of the BSB and the NTP point of contact for Tox21. “This was the most appropriate time to have this review as we move from our Phase I proof-of-principle efforts to Phase II, and from screening a library of approximately 2,800 compounds to one of more than 10,000 compounds, in addition to our other activities” ([see interview](#)).



Novak, who spent his final meeting as Board chair, listened thoughtfully during the two days of presentations. (Photo courtesy of Steve McCaw)



Tice, shown at an earlier talk about Tox21 high-throughput screening, was the keynote speaker during the review of BSB and Tox21. (Photo courtesy of Steve McCaw)

	Linked video: Tice introduces Tox21 and the partnership that is moving it forward to reality (2:03)
(Launches in new window)	
Download Media Player:  Quicktime	

Tox21 was established in 2008 with a [Memorandum of Understanding](#) (MOU) that was expanded in July 2010 to include the [FDA](#) along with the original partners, NIEHS/NTP, EPA, and the National Institutes of Health Chemical Genomics Center (NCGC). Each partner has an agency point of contact as its lead representative, and is represented by a co-chair for each of the four Tox21 Working Groups: Chemical Selection, Assays and Pathways, Informatics, and Targeted Testing.

The BSC was briefed on progress by each of the Tox21 partners and Working Groups, and was updated on BSB activities directly related to Tox21, including the *C. elegans* “Worm Tox” Screening Facility, a collaboration with University of North Carolina at Chapel Hill that is probing mechanisms of inter-individual susceptibility to toxicants with population-based experimental approaches, a project exploring mining the NTP Tissue Archives for gene signatures, a program that is developing a bioinformatics-based approach to identify assays that query human health effects, and the mouse methylome project, which is being conducted by the Host Susceptibility Group within the BSB.

BSC Chair Raymond Novak, Ph.D., who is corporate director of research at Shriners Hospitals for Children International, said the board's reaction to the BSB/Tox21 review was, overall, very enthusiastic. "They were excited about all of the different components that were brought together in a cohesive manner, the communication and the coordination that had occurred for that to take place, and the incredible opportunities that exist to achieve a final product that could be directed toward a rational approach to risk assessment in human populations," he said. As Novak explained, the bottom line is that "if the NTP and all of these other resources can't get predictive toxicology to work, then no one can."

The next BSC meeting is scheduled for April 12-13, 2011.

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



"Board member James Sherley, M.D., Ph.D., from the Boston Biomedical Research Institute, commented on one of the BSC meeting presentations. (Photo courtesy of Steve McCaw)



David Dix, Ph.D., updated the BSC on Tox21 developments and activities at the EPA. (Photo courtesy of Steve McCaw)



Relishing the opportunity to "do science" for two days, Birnbaum asked many questions over the course of the BSC meeting. (Photo courtesy of Steve McCaw)

In other business

During her update to the Board on Institute developments, NIEHS/NTP Director Linda Birnbaum, Ph.D., announced the appointments of Richard Woychik, Ph.D., as the new deputy director of NIEHS ([see story](#)) and Gwen Collman, Ph.D., as director of the Division of Extramural Research and Training ([see story](#)). She also presented retiring board members Tracie Bunton, D.V.M., Ph.D., Edward Carney, Ph.D., Russell Cattley, Ph.D., William Janzen, Ph.D., and departing chair Novak with certificates of service, as she thanked them for their contributions to NTP.

Looking back on his tenure with the NTP BSC, Novak said, “It was a great experience. It offered an opportunity to provide inputs and make comments on various studies that were either being proposed or had been completed, for which a determination had to be made. It was also an opportunity to make a difference, and to make a difference from a long-term perspective.”

In other business, the BSC voted to support a Contract Concept for a program to perform sperm count and vaginal cytology evaluations on tissues obtained from animals in the NTP’s 90-day toxicity studies. The Board also reviewed NTP Testing Program Concepts regarding men working with bisphenol A, toxicological approaches to assessing complex mixtures, N-butylbenzenesulfonamide, and selected flame retardants ([see meeting materials online](#)).

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Tice talks Tox21

By Ernie Hood

As a follow-up to the BSC review of the NTP Biomolecular Screening Branch (BSB), Chief Ray Tice, Ph.D., responded to several questions about Tox21 and its future directions.

One of the threads that emerged during the meeting was the need to communicate with the lay public about Tox21. Given the platform to do so, what would you most like to put forth?

Basically, we want the lay public to understand the purpose and goals of Tox21; to appreciate that, currently, we are conducting a research program since we do not yet have enough information to demonstrate the adequacy of using data from assays using cultured cells and lower organisms to identify compounds that are harmful to humans, other animals, and the environment; and to understand it will likely be several to many years before there is sufficient data for the kind of critical evaluation needed.

How important is Tox21 to NTP and NIEHS? What role does it play, and how do you think that will evolve?

The purpose of Tox21 is to support the evolution of toxicology from a predominantly observational science at the level of disease-specific models, to a predominantly predictive science focused upon a broad inclusion of target-specific, mechanism-based, biological observations using cultured cells, 3D model tissues, and phylogenetically lower organisms. This can only be accomplished if we utilize the complementary expertise and capabilities of multiple organizations — no single organization could succeed in this endeavor by itself. The knowledge bases and informatics tools developed to support this effort will be used by the NIEHS/NTP

to gain a much better understanding of the relationship between compounds, genes, pathways, and disease, in order to prioritize compounds for more comprehensive testing, to identify mechanisms of action, and to develop predictive models of human disease.

How has the interagency collaboration among the partners worked out?

Absolutely great. We are all committed to a common goal, and where our respective approaches differ, they differ in a way that is complementary rather than in conflict. It's difficult for me to imagine working with a better group of scientists.

It seems from the presentations at the BSC meeting that Tox21 has made remarkable progress in a very short period of time.

I agree. We have been working on Tox21-related efforts since late 2004, but it's only since the first MOU was signed in February 2008 that we established a formal infrastructure to integrate our respective Tox21 activities. Given that, I believe that our success to date has largely been due to, first, the 2007 release of the National Academy of Sciences report called "Toxicity Testing in the 21st Century: A Vision and a Strategy." Second, I would cite the very active support of senior management at the different federal agencies participating in Tox21, along with the commitment of the Tox21 staff to a common goal. Finally, there has been the recognition of the international scientific community that this is an effort worthy of support.

I do think we're making faster progress than I originally anticipated, but like all great endeavors, we might encounter a major obstacle tomorrow or the next day that will require brand new approaches for moving Tox21 forward.

What's next for Tox21?

We plan to expand our interactions with other individuals and organizations, whether government, academic, or private, in order to accelerate the acquisition of data and the development of new tools. We will keep focused on our overall Phase II strategy, while remaining flexible in the event that a major advance in basic biology, medicine, or toxicology might necessitate a shift in focus. We will continue to make sure that all of the data we collect is made openly accessible to the international scientific community as quickly as possible. And, of course, we will continue to try to make sense out of the data we have collected.

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

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Birnbaum addresses Mt. Sinai autism workshop

By Eddy Ball

NIEHS/NTP Director Linda Birnbaum, Ph.D., was the keynote speaker among a group of presenters who gathered Dec. 8 for a scientific workshop at the New York Academy of Medicine.

The workshop, "[Exploring the Environmental Causes of Autism and Learning Disabilities](#)," brought together NIEHS grantees and partners in the ongoing search for ways to prevent autism. The event was hosted by NIH-funded researchers at Mount Sinai School of Medicine (MSSM), led by MSSM Chairman of the Department of Preventive Medicine Philip Landrigan, M.D., in partnership with Autism Speaks, represented by Director of Research for Environmental Sciences Alycia Halladay, Ph.D.

Along with principal investigators on four autism studies ([see text box](#)), speakers in the first part of the workshop included representatives of the advocacy group Autism Speaks, the Centers for Disease Control and Prevention (CDC), and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD).

In the second half of the workshop, members of the MSSM faculty presented resources for autism and learning disabilities research, and Landrigan concluded with a talk about the challenges ahead in autism research.

The NIEHS commitment to autism research

As the keynote presentation, Birnbaum's talk, "What Research is NIEHS Supporting into Environmental Causes of Autism and Learning Disabilities?" underscored the deep commitment to autism research by NIEHS, which she described as "the only Institute of NIH that focuses on public health and prevention."

Birnbaum described the direct investment of \$30 million in animal and human studies of neurodevelopment by NIEHS. She also pointed to research efforts in all the different components of NIEHS that contribute to advancing the science relevant to neurodevelopmental disorders, such as basic research in neurotoxicology and exposure science that will be essential for understanding and informing human studies in autism.

"About two-thirds of these projects are human studies, with the rest laboratory based mechanistic studies," Birnbaum explained. "The support mechanisms range from small exploratory grants to individual investigator-initiated R01s [research project grants] to large, multi-project grants."

The impressive list of highlights began with the Children's Environmental Health and Disease Prevention Program, one of the largest research investments by NIEHS in autism and neurodevelopment. Birnbaum said that six of the 14 centers are focused wholly, or in part, on neurodevelopmental outcomes — the University of California (UC), Davis; UC, Berkeley; University of Washington; Columbia University; and University of Illinois at Urbana-Champaign, which houses an exploratory center.

Along with directly funding neurodevelopmental research, Birnbaum continued, NIEHS, together with several other NIH institutes, funded the Early Autism Risk Longitudinal Investigation (EARLI) network study, as part of the trans-NIH Autism Centers of Excellence (ACE) program. She followed with an impressive list of findings by Center researchers and individual investigators.

Turning to other components of NIEHS, Birnbaum talked about studies by the National Toxicology Program and basic mechanistic research in the intramural program's Laboratory of Neurobiology.



Birnbaum is raising awareness among advocacy groups and scientists that virtually every kind of research funded by NIEHS has a bearing on neurodevelopment. (Photo courtesy of the University of Illinois)



Landrigan is the principal investigator for one of the National Children's Study vanguard centers and a tireless advocate for children's environmental health. (Photo courtesy of Mount Sinai School of Medicine)

In closing, Birnbaum looked to the future as NIEHS builds upon its successes to move ahead in concert with its partners. “Future NIEHS activities in neurodevelopment will emphasize priorities identified through strategic planning and coordination with other federal agencies, the meaningful involvement of affected communities, and the translation of findings to public health and prevention,” she concluded.

Autism research project reports

Also presenting at the workshop were four principal investigators of ongoing studies of the causes of autism:

- Irva Hertz-Picciotto, Ph.D., professor and chief, Division of Environmental and Occupational Health, Department of Public Health Sciences at the University of California, Davis — “Environment and Autism: State of the Science and the CHARGE [Childhood Autism Risks from Genetics and Environment] Study” — funded by NIEHS ([see story](#))
- Craig J. Newschaffer, Ph.D., professor and chairman, Department of Epidemiology and Biostatistics at Drexel University School of Public Health — “The EARLI [Early Autism Risk Longitudinal Investigation] Network” — funded partially by NIEHS as an NIH Autism Center of Excellence ([see story](#))
- Young-Shin Kim, M.D., Ph.D., assistant professor, the Child Study Center at Yale University School of Medicine — “The Korean Autism Study” — funded by the [Simons Foundation](#)
- Christine Roth, visiting research scholar in the Department of Epidemiology of the Mailman School of Public Health at Columbia University — “The Norwegian Mother and Child Cohort Study” — supported in part by [NIEHS](#)



Hertz-Picciotto has looked at several factors, including mitochondrial disorders and proximity to high-volume traffic, that could help trigger autism. (Photo courtesy of the University of California Regents)



Newschaffer and colleagues will follow an enriched-risk pregnancy cohort of up to 1,200 participants over a three-year period. (Photo courtesy of Drexel University)

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Balbus reports on US federal climate change and health initiatives

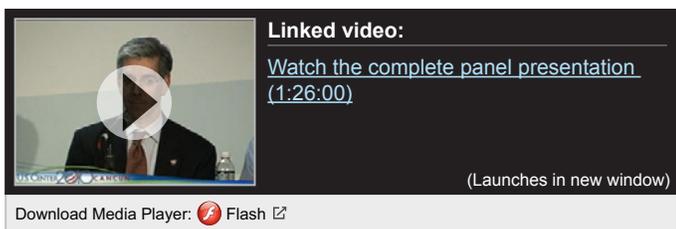
By Matt Goad

NIEHS Senior Advisor for Public Health [John Balbus, M.D.](#), highlighted new efforts of cooperation on climate change and public health as part of a side event he organized at the United Nations Climate Change conference Dec. 3.

Balbus was the second of three experts ([see text box](#)) speaking before a live audience of nearly 50 attendees as part of COP16/CMP6, the 16th edition of the Conference of the Parties of the United Nations Framework Convention on Climate Change (COP) and the sixth Conference of the Parties serving as the meeting of the Parties to the Kyoto Protocol (CMP) meeting in Cancun, Mexico. The event was also webcast to a large virtual audience worldwide.



As NIEHS lead on climate change, Balbus is a key player in U.S. Department of Health and Human Services, trans-NIH, and interagency efforts to improve global public health. (Photo courtesy of John Balbus)



In his presentation, Balbus described the creation of a new Interagency Crosscutting Group on Climate Change and Human Health within the [U.S. Global Change Research Program \(USGCRP\)](#) that is coordinating and building capacity within the federal government for public health activities related to climate change, and also highlighted other related public health activities under way within the United States and internationally.

“We’re starting to see, at least, broader engagement and broader involvement across the traditional health research apparatus in the United States,” Balbus said with a note of cautious optimism. He then pointed to several examples of increased efforts by federal agencies to work together to study the potential impact of climate change on global public health:

- An NIEHS-led funding opportunity begun this fall focused on population vulnerability to impacts of climate change on human health. This effort involves 13 NIH Institutes and Centers.
- In 2009, the National Institutes of Health released the first dedicated funding opportunity for climate change and health. Five projects were funded, as part of the American Recovery and Reinvestment Act ([see story](#)).



Ebi, left, kicked off the panel presentation as Balbus, center, and von Hildebrand waited for their turns at the podium. (Photo courtesy of John Balbus)

- Also in 2009, the Centers for Disease Control and Prevention launched its own climate change program.
- On Earth Day, 2010, the NIEHS-led *ad hoc* Interagency Working Group on Climate Change and Health released A Human Health Perspective on Climate Change, a white paper organized along the lines of how biomedical researchers and health professionals think – by categories of disease outcomes ([see story](#)).

These developments are in addition to work the federal government was already doing, Balbus continued, including early warning of famine across the globe, regional monitoring of drought, and a malaria early warning program that is a joint effort of the National Aeronautics and Space Administration and the U.S. Agency for International Development.

Balbus hypothesized that sharing efforts of U.S. agencies to work together might help the global health community to work together.

“As a physician, as a public health professional, and especially as a parent,” Balbus said, “I strongly believe the public health community has to organize itself to help accomplish three things: The first thing is to help limit the extent of climate change; the second is to anticipate those adverse health impacts that may be unavoidable, and to try to either prevent them in their full extent or at least lessen their severity; and then the third, just as importantly, ... is for the public health community to identify those opportunities for improving public health that are going to arise in dealing with climate change.”

The federal government’s work on climate change underwent a major shift in 2007, Balbus said. Before 2007, the emphasis was on determining whether climate change existed, whether human activities were causing it, and whether it could be quantified. By 2007, researchers were agreeing that the answer to these questions was yes.

The main issues now, Balbus continued, are determining the urgency, timing, and severity of climate change; determining if we have the means to actually mitigate greenhouse gas emissions to slow and ultimately reverse the process; and what we can do right now to adapt to these changes, including how to protect health.

(Matt Goad is a contract writer with the NIEHS Office of Communications and Public Liaison.)

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Rounding out the panel of experts

In addition to Balbus, the panel included two high-profile leaders in efforts to understand and ameliorate the impact of climate change on human health:

- Kristie Ebi, Ph.D., executive director of the [Intergovernmental Panel on Climate Change \(IPCC\)](#) Working Group II Technical Support Unit, surveyed the state of the science on climate change health impacts and the potential for both co-benefits and adverse health impacts from societal responses to climate change.
- Alexander von Hildebrand, Ph.D., advisor for Sustainable Development and Environmental Health in the [Pan American Health Organization](#), reported on collaborations in Latin America to help populations stay healthy as climate changes. As manifestations of global climate change become more apparent, it is critical that countries understand and commit to minimizing public health consequences.

NIEHS holds public partners meeting

By Matt Goad

The annual NIEHS Public Interest Partners meeting Dec. 9 in Washington, D.C., was capped by a free-wheeling afternoon of open discussions with NIEHS/NTP Director Linda Birnbaum, Ph.D.

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 community 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.

Presentations and informal discussion

The meeting opened with three morning presentations on [NIEHS activities](#) in the aftermath of the Gulf oil spill by the Institute's major components ([see related story](#)):

- The GuLF Study, reported by Dale Sandler, Ph.D., chief of the Epidemiology Branch
- New research grant opportunities, presented by Claudia Thompson, Ph.D., acting chief of the Susceptibility and Population Health Branch
- National Toxicology Program (NTP) studies, described by Chris Weis, NIEHS toxicology liaison.

After the presentation, one partner, Leyla McCurdy, expressed her thoughts: "I'm sitting here listening to the three-prong approach. This is the NIEHS we know and love."

Birnbaum then opened the discussion portion of the meeting with a list of highlights from topics of NIEHS research on complex diseases. Studies on diabetes, for instance, include the role of bisphenol A in promoting diabetes, Birnbaum told the partners.

She explained that work on asthma includes a study of children exposed to high levels of traffic-related air pollution at school and home; a study of genetic susceptibility to asthma being conducted in Mexico City; and the Head-off Environmental Asthma in Louisiana (HEAL) study examining the effects of post-Hurricane Katrina mold and indoor allergens on children with asthma.



The NIEHS Public Interest Partners meeting gave participants an opportunity to mingle, to talk, and, most importantly for NIEHS representatives, to listen. (Photo courtesy of John Schelp)

“These are just a small sampling of the achievements and public health impacts generated by environmental health scientists across the country,” Birnbaum said. “Hopefully, you have a good sense of the work we support at NIEHS and how this work can positively affect the health of your constituents. Let me end by saying that we look forward to supporting and working with scientists, health care providers, and advocates to continue the success of our work, to better understand how the environment affects our health, and to develop effective prevention strategies to protect public health.”

She then opened the discussion portion of the meeting by saying, “OK, let me stop. Communication with our partners is a two-way street. I want to listen. So let’s talk.”

After the gathering, one partner said it was refreshing to just talk and not sit in a dark room looking at PowerPoint presentations all day.

(Matt Goad is a contract writer with the NIEHS Office of Communications and Public Liaison.)



Jeanne Rizzo, director of the Breast Cancer Fund, left, and Patrick Wildman of the ALS (Amyotrophic lateral sclerosis) Association, had an opportunity to share their successes and challenges in a forum that brought together people who normally have little opportunity to interact. (Photo courtesy of John Schelp)



Left to right, Leyla McCurdy of the National Environmental Education Foundation, Lynne Cannon of the Learning Disabilities Association of America, Kari Christianson of DES (diethylstilbestrol) Action USA, and Betty Mekdeci of Birth Defects Research for Children participate in a more serious moment of the meeting. (Photo courtesy of John Schelp)



The informal discussion also set the tone for good will. Shown left to right, Betty Mekdeci, Partners co-chair, Birnbaum, and NIEHS Outreach Coordinator Ericka Reid enjoy one of the lighter moments of the give and take. (Photo courtesy of John Schelp)

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Clinical Research Unit enhances intramural research

By Robin Arnette

The NIEHS [Clinical Research Unit \(CRU\)](#) allows the public to participate in clinical trials and also provides Institute researchers with opportunities to augment their basic research with human samples. Both endeavors contribute to understanding how environmental exposures potentially influence human disease.

If you are interested in participating in a clinical research trial at the CRU, please visit the [Join a Health Study or Clinical Trial](#) Web page or contact the NIEHS CRU admissions desk at 919-541-9899.

During the first week of December 2010, the CRU enrolled its 500th study participant and experienced its busiest week to date, with 42 people volunteering to take part in a clinical study. Darryl Zeldin, M.D., acting director of the [Clinical Research Program](#), said that during the first eight months after its grand opening on July 27, 2009, the CRU saw two or three participants a week, but he believed the totals steadily increased because more NIEHS scientists initiated clinical research projects at the facility.

“When the CRU was first envisioned years ago, everyone thought it was going to be a unit that primarily serviced the physicians on staff,” Zeldin explained, “but, if you look at the people who are using the unit now, many of them are Ph.D.s. Their CRU work allows them to translate what they’ve done for many years at the [research] bench to humans.”

CRU scientists have varied backgrounds

The CRU currently serves 13 tenured and 7 tenure-track investigators, with the Ph.D.s outnumbering the M.D.s two to one. Zeldin expects the number of Ph.D. researchers to grow, especially since many of the studies have generated a lot of useful data so far.

One of those researchers is Mike Fessler, M.D., head of the [Host Defense](#) and [Environmental Innate Immunity](#) Groups. His research has used human monocyte-derived macrophages to dissect a novel innate immunity signaling pathway triggered by apolipoprotein A-I. The work has resulted in the first published report based on CRU data and appears in the journal *Cell Metabolism* ([see text box](#)).

Leader of the Chromosome Stability Group [Mike Resnick, Ph.D.](#), uses blood cells and alveolar macrophages to study the induction of the Toll-like receptor (TLR) genes by p53 and DNA damage. He and two fellow CRU researchers have submitted a paper that is currently under review by a leading peer-reviewed journal. Resnick said that his group started using human cell lines 10 years ago, and that the opening of the CRU came at the perfect time. “Our research led us to consider using clinical samples, just as the CRU was taking shape,” he added.



Zeldin said that in addition to using the website to recruit study participants, the CRU staff travels to health fairs in different communities to recruit volunteers. (Photo courtesy of Steve McCaw)



Besides being medical director of the CRU, Garantziotis carries out his own clinical studies there, examining the effects of nanotechnology on human health. His work involves exposing human macrophages and bronchial epithelia cells to nanomaterials and comparing the cells from healthy individuals to those with asthma. (Photo courtesy of Steve McCaw)

Ron Mason, Ph.D., heads the Free Radical Metabolism Group, and his work with human blood cells has identified sulfite radicals that contribute to oxidative protein damage in asthma and allergic inflammatory disorders. He is preparing a manuscript that he hopes to publish sometime in spring 2011.

NIEHS/NTP Director Linda Birnbaum, Ph.D., NTP Associate Director John Bucher, Ph.D., and Acting Director of the NTP Center for the Evaluation of Risks to Human Reproduction (CERHR) Kristina Thayer, Ph.D., plan to examine the endocrine disruptor bisphenol A (BPA) after oral exposure.

Birnbaum said, “We are interested in understanding how rapidly BPA is eliminated from the body and whether we can find any BPA present in the blood of subjects after treatment.”

The CRU staff makes it all work

CRU-supported researchers interact with Medical Director Stavros Garantziotis, M.D., and his hard-working staff of six — two federal employees, biologists Annette Rice and Jamie Marshburn who process and distribute samples, and four contract personnel, nurse Brenda Yingling, R.N., study manager Neha Mehta, study coordinator Lisa Murphy, and receptionist Nicole Edwards.

According to Garantziotis and Zeldin, the CRU has reached its maximum capacity of 40–45 study participants a week, but, starting in January 2011, they’ll add another nurse and study coordinator to accommodate the increased need. “The new staff additions will allow us to step up recruiting efforts and could potentially push us up to 50–100 study participants a week,” Zeldin said.

Studies based on research in the CRU

- Smoak KA, Aloor JJ, Madenspacher JH, Merrick BA, Collins JB, Zhu X, Cavigliolo G, Oda MN, Parks JS, Fessler MB. 2010. Myeloid differentiation primary response protein 88 couples reverse cholesterol transport to inflammation. *Cell Metab* 11(6):493-502. (impact factor 17.350)
- Menendez D, Shatz M, Smoak KA, Garantziotis S, Fessler MB, Resnick MA. The Toll-like receptor gene family is integrated into human DNA damage and p53 networks. Accepted with revisions, *PLoS Genetics* (impact factor 9.532)
- Rangelova K, Rice AB, Garantziotis S, Mason RP. Formation of reactive sulfite-derived free radicals by the activation of human neutrophils. An ESR study submitted



Birnbaum said that her clinical pharmacokinetic study of BPA is a natural extension of some of the work that she’s done in the past. (Photo courtesy of Steve McCaw)



Fessler wrote the first Institutional Review Board (IRB) protocol allowing for human subjects research at the CRU. The protocol detailed how to collect blood cells from healthy volunteers. He has also been a member of the NIEHS Clinical Advisory Council, an advisory board that reviews clinical research proposals. (Photo courtesy of Steve McCaw)



Resnick said that the CRU was solely responsible for helping him develop a clinical focus for his research. (Photo courtesy of Steve McCaw)

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Mason's current affiliation with the CRU isn't his first experience with clinical research. Before coming to NIEHS, he performed clinical studies at the Veteran's Administration Medical Center at the University of Minnesota-Minneapolis. (Photo courtesy of Steve McCaw)

NIEHS completes draft of metrics manual

By Matt Goad

NIEHS-funded research helps advance public health in many ways, and the [Partnerships for Environmental Public Health \(PEPH\)](#) program is helping grantees measure just how many ways. Now available for public review, the new [PEPH Evaluation Metrics Manual](#) is designed to help grantees identify and measure the key activities, outputs, and impacts of their partnership work.

“We are helping grantees understand and map out what their influence is and demonstrate the effects of their research,” said Christie Drew, Ph.D., chief of the NIEHS [Program Analysis Branch \(PAB\)](#).

PEPH is letting NIEHS employees and grantees get a look at the first draft of the manual on Jan. 10 from noon to 1:30 p.m. in the Rodbell Auditorium at NIEHS. The session is open to all NIEHS and U.S. Environmental Protection Agency staff, as well as the general public. During the presentation, Drew will provide an overview of the manual and facilitate discussions to obtain feedback on the content and metrics.

Over the next few months, PAB will present the manual to several other NIH centers, as well as the Centers for Disease Control and Prevention's evaluation workgroup. The PAB staff will also conduct webinars for groups such as the Association of State and Territorial Health Officials and National Environmental Health Association.

“This is the first draft of the manual,” said Kristi Pettibone, an evaluator with the PAB. “What we want to do now is to take it out to the folks who are doing this work, and get their thoughts and ideas about how to make it even better.”

Measuring success

During the first PEPH grantee meetings, researchers talked about the challenges associated with measuring and documenting their successes in environmental public health activities. PAB began drafting the manual in June 2009 in response to these challenges. “Commonly, scientists measure the success of their research by counting their publications, but this is not the only way,” Drew said.

As the accountability culture of Washington expands, the need for evaluation also expands, and people want to be able to show what grants have accomplished.

Other metrics that PEPH grantees could use to demonstrate achievements include documenting testimony before a legislative committee; interactions with the target audience; activities; outcomes and impacts related to partnership building; product development and dissemination; and education and training activities.

Not all about numbers

“The science of measurement is not all about numbers,” Drew explained. “We have worked hard in the manual to focus on narrative and descriptive metrics, in addition to the numbers.”

Grantees sometimes think they have to demonstrate major changes, such as reductions in asthma cases or school absence rates. But it can be difficult for grantees to measure such long-term goals, according to Drew. The Evaluation Metrics Manual shows grantees how to identify and measure key activities and short-term outputs associated with their projects. This enables grantees to show progress along the way to reaching their long-term goals.

“Although we have provided lots of ideas and metrics related to environmental public health activities,” Drew said, “we want grantees to understand that these measures are just examples of some of the many ways to implement and measure the environmental impact of their work.”

(Matt Goad is a contract writer with the NIEHS Office of Communications and Public Liaison.)

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Oil spill update – NIEHS activities in the Gulf

By Christine Flowers

The Gulf oil spill may be largely out of the headlines these days, but NIEHS continues its efforts to better understand the impact on the health of the people of the region. NIEHS has activated programs throughout the institute to provide timely and responsive services following the Deepwater Horizon Gulf oil spill:

- **Safety Training** – Within days of the explosion, the NIEHS Worker Education and Training Program facilitated safety training for more than 100,000 cleanup workers.



Drew heads a branch in the NIEHS Division of Extramural Research and Training that analyzes the effectiveness of grants ranging from basic research to environmental justice. (Photo courtesy of Steve McCaw)

- **GuLF Study** – The NIEHS Epidemiology Branch is heading the NIH GuLF (Gulf Longitudinal Follow-up) Study on the long-term health effects of the oil spill.
- **Toxicology Research** – The NIEHS National Toxicology Program, working together with federal partners, is conducting studies to better understand the chemistry, biological fate, and toxicological effects of crude oil and dispersant components and breakdown products.
- **Research Consortia Funding** – NIEHS will fund grants for researcher-community partnerships to address the needs of affected communities.
- **Other Research Grants** – The NIEHS grants program currently supports research and outreach efforts on the health effects of exposure to oil and dispersants.

Details are available [online](#).



NIEHS Epidemiology Branch Chief Dale Sandler, Ph.D., is principal investigator for the GuLF Study. (Photo courtesy of Steve McCaw)

A long-term presence in the Gulf

NIEHS has hosted a series of community forums, stakeholder visits, webinars, and instructional meetings throughout the five-state Gulf region in order to promote awareness, participation and coordination for all these programs among local residents, state and local health departments, regional universities and researchers, and federal agency partners.

The [GuLF Study](#) will focus on exposure to oil and dispersant products and potential health consequences such as respiratory, neurobehavioral, carcinogenic, dermal, and immunological conditions. The study will also evaluate mental health concerns and other oil spill-related stressors such as job loss, family disruption, and financial uncertainties.

NIEHS will invite approximately 55,000 people to participate in the study. Building on an extensive roster of cleanup workers developed by the National Institute for Occupational Safety and Health, the NIEHS will supplement the roster with other lists of workers compiled by BP, contractors, and community organizations. The study will enroll cleanup workers, volunteers, and community members with varying levels of potential exposure including workers involved in oil burning, skimming and booming equipment decontamination, wildlife cleanup, and also those with lower exposure such as shoreline cleanup workers.

The study will also recruit some people who completed the worker safety training, but did not do any clean-up work. Members of the U.S. Coast Guard, U.S. National Guard, and other federal agencies who were called to respond will also participate in the GuLF Study.

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NIEHS scientists join tour of Morehead Planetarium

By Sophie Bolick

NIEHS women scientists joined their colleagues for a special behind-the-scenes tour of the Morehead Planetarium at the University of North Carolina at Chapel Hill on Nov. 17.

Organized by Rho Tau, the local chapter of Graduate Women in Science (GWIS), the tour gave Morehead staff members an opportunity to showcase the science outreach resources available for scientists at NIEHS and elsewhere in the Triangle.

Among the NIEHS scientists in attendance were Staff Scientist Harriet Kinyamu, Ph.D., and Intramural Research Training Award Fellow Kelly Mercier, Ph.D. Mercier is one of the founders of the Rho Tau chapter of GWIS, an interdisciplinary society of scientists who encourage and support women through outreach and networking activities to enter and achieve success in science. Membership includes women in scientific roles ranging from graduate students and full professors to pharmaceutical company executives.

An active comprehensive science center

[Morehead Planetarium](#) is an active comprehensive science center, with activities for all ages. Live shows in the GlaxoSmithKline Fulldome Theater are the centerpiece of a wealth of resources available to the citizens of North Carolina. Demonstrating the successful merger of cutting-edge technology and science, Morehead staff enthusiastically previewed one of their new digital planetarium shows.

While there are plenty of hands-on activities on site, Morehead staff takes science to students around the state through the DESTINY (Delivering Edge-cutting Science Technology and Internet across North Carolina for Years to come) program. In “Brand Name Genes,” one of the DESTINY modules available to North Carolina educators, students learn about biotechnology by using the polymerase chain reaction (PCR) to detect the BRCA mutation in breast cancer — a marker of risk discovered in 1994 by NIEHS researchers in collaboration with a scientist at the University of Utah. This real-life scenario builds the scientific skills of students, while also teaching critical thinking skills.

Scientists’ involvement is pivotal to success

“Scientists are critical to the success of Morehead’s programs,” says Denise Young, director of Education Programs at Morehead Planetarium. “Behind the scenes, they provide content expertise and review for scientific accuracy.”

However, the greatest benefit for both scientists and the public are the opportunities for interaction Morehead offers. “Many scientists are reinvigorated by explaining what they do and why it’s so cool.” Young continued, “One scientist actually told us that by explaining his research to our multimedia folks, he grew to understand his research in a new way.”



UNC
MOREHEAD PLANETARIUM
AND SCIENCE CENTER



“The Planetarium offers unique opportunities for scientists to become better communicators,” says Harriet Kinyamu, Ph.D., staff scientist with the [Chromatin and Gene Expression Group](#) in the Laboratory of Molecular Carcinogenesis. (Photo courtesy of Steve McCaw)

While Rho Tau provides many networking events for local women scientists, this is the first educational event sponsored by the organization. According to Mercier, “It has always been the desire of the Rho Tau chapter to not only provide the means for women scientists to network, but also expose our members to different types of science.” She and Young tailored the evening to benefit the visiting scientists. “We came up with a program that would not only show our members how their facility is managed, but also how we can help as experts in the community,” stated Mercier.

(Sophie Bolick, Ph.D., is a postdoctoral fellow with the Molecular and Genetic Epidemiology Group in the Laboratory of Molecular Carcinogenesis.)



Mercier is a postdoctoral fellow with the [Nuclear Magnetic Resonance Group](#) in the Laboratory of Structural Biology, and she currently serves as President of Rho Tau.

(Photo courtesy of Steve McCaw)



“Visitors love interacting directly with scientists.” Young continues, “These interactions leave people with a more realistic impression about what science is and why it’s so fun and important.” (Photo courtesy of UNC)

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Hughes represents NIEHS at White House forum

By Ed Kang

NIEHS Worker Education and Training Program Director Chip Hughes joined top-level policy and practice leaders Dec. 15 in Washington, D.C. for a historic collaboration on environmental justice issues.

The one-day forum, held in the Eisenhower Executive Office Building and broadcast live on the Internet, allowed a national audience to interact with the highest levels of government on green jobs and energy, sustainability and development, and healthy communities. The forum focused on the current administration’s commitment to ensuring that overburdened and low-income communities have the opportunity to enjoy the health and economic benefits of a clean environment.

Hosted by Nancy Sutley, chair of the White House Council on Environmental Quality, the forum assembled more than 100 environmental justice leaders from across the country with U.S. Environmental Protection Agency (EPA)

Administrator Lisa Jackson, Attorney General Eric Holder, Secretary of the Interior Ken Salazar, Secretary of Labor Hilda Solis, Secretary of Health and Human Services (HHS) Kathleen Sebelius, and Secretary of Homeland Security Janet Napolitano.



“The meeting brought not only agency leaders together, but also community institutions, as a meaningful display of knowledge-sharing,” said Hughes. He was joined at the meeting by NIEHS grantees, including Robert Bullard, Ph.D., director of [Clark Atlanta University’s Environmental Justice Resource Center](#), and Beverly Wright, Ph.D., director of the [Deep South Center for Environmental Justice at Dillard University](#).

The unfinished business of environmental justice

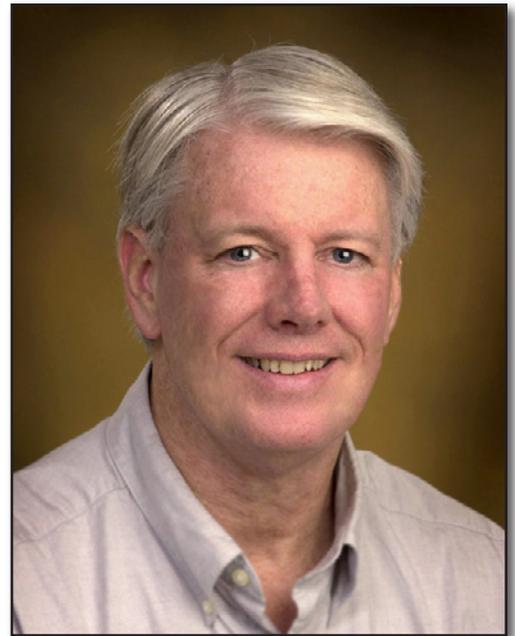
To open the meeting, Jackson reminded the audience that while issues of disparate impacts to low income and minority communities are not new, “environmental justice is our unfinished business.” Since her appointment, Jackson has made environmental justice a priority at EPA, listing it as one of seven strategic priorities for the agency. As part of the “Environmental Justice Tour,” she has joined members of the Congressional Black Caucus on visits to areas facing environmental distress.

“We work to make environmental justice part of everything we do. The federal government has a particular responsibility to underserved communities,” Jackson stated. Her agency’s [Plan EJ2014](#) provides a roadmap for incorporating environmental justice into the core work of EPA.

Healthy communities and place-based initiatives

Secretary Sebelius spoke openly about the health implications of environmental justice. “Health hasn’t always been the first issue you associate with environmental justice,” she said. “There’s a new understanding that some of the most important steps we can take to improve health have nothing to do with treating a disease or injury - they have to do with preventing those diseases and injuries in the first place.”

Sebelius took the forum as an opportunity to preview new health reform legislation, a \$15 billion Prevention and Public Health Fund that will invest in programs across the country to transform community health. The development of comprehensive strategies from promoting better nutrition for children to creating safer neighborhoods where people can walk can create empowerment zones that ultimately improve health.



Environmental justice is an important part of the worker safety and training emphasis in programs Hughes and his staff oversee. (Photo courtesy of Steve McCaw)



Under Jackson’s leadership, environmental justice has become a higher priority for EPA. (Photo courtesy of EPA)

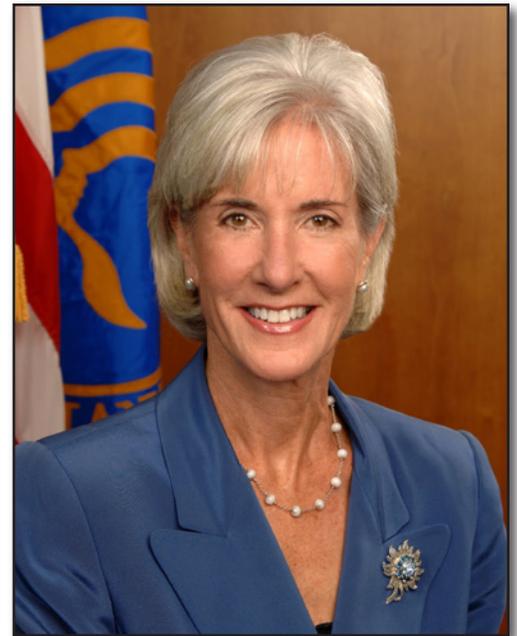
Sebelius also recognized research into the connections between environment and health, and the work of NIEHS. “We’re putting a special focus on collaborating with minority communities, whose health often suffers the most from environmental factors,” she said.

“It shows that environmental justice is now a priority,” said Hughes. “Agencies have been tackling environmental justice issues, but we now have more opportunities to collaborate and share effective strategies.”

NIEHS staff and leadership, including Gwen Collman, Ph.D., John Balbus, M.D., Chip Hughes, Liam O’Fallon, and Sharon Beard, have been working with the HHS Office of the Assistant Secretary for Health to update and revise a Department-wide strategy addressing prevention and environmental justice issues.

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

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Sebelius underscored the importance of primary prevention in the pursuit of environmental justice. (Photo courtesy of HHS)

NIEHS helps launch Healthy People 2020

By Matt Goad

As the U.S. Department of Health and Human Service’s (HHS) Healthy People initiative looks to its third decade of striving for a society in which all people live long, healthy lives, it turns to the latest means of communication to get out its message.

On Dec. 2, [Healthy People 2020](#) kicked off with a live webcast and a coinciding Twitter discussion, putting a greater emphasis on new technologies to educate a broader audience about a range of health topics, including the role of environment factors.

NIEHS takes part in the initiative as the co-lead agency on the [Environmental Health](#) topic area and is one of three National Institutes of Health (NIH) agencies leading the [Respiratory Diseases](#) topic area. Both of these topic areas have a clear relationship to the NIEHS mission. For example, the Environmental Health topic area has objectives that span topics ranging from healthy homes and communities to global health.

The NIEHS representative for Healthy People, Program Analyst Bill Jirles of the Institute’s Office of Policy, Planning, and Evaluation, said the Web and cell phones would make the project more accessible and more responsive to the public.

“Previously organizers provided big books that contained the Healthy People objectives, which were hundreds of pages in length,” Jirles explained.

Healthy People 2020 will rely instead on its [Website](#) to carry that information.



“This iteration will be a lot more dynamic,” Jirles continued. “It will be easier to make changes throughout the process since the objectives are all Internet-based, rather than making official changes every few years. Now we’ll be able to make official updates to the objectives on the Web pages in a fraction of the time.”

Since 1990, when work began on Healthy People 2000, the Healthy People initiative has looked to improve the nation’s health by working across HHS agencies to identify nationwide health improvement priorities and taking action to strengthen policies and improve practices that address those priorities.

“It’s been something that NIEHS and NIH have supported for a long time,” Jirles said.

For the third iteration, Healthy People 2020, the project identified [42 topic areas](#). The Centers for Disease Control and Prevention will track progress on these 42 topic areas as the decade progresses.

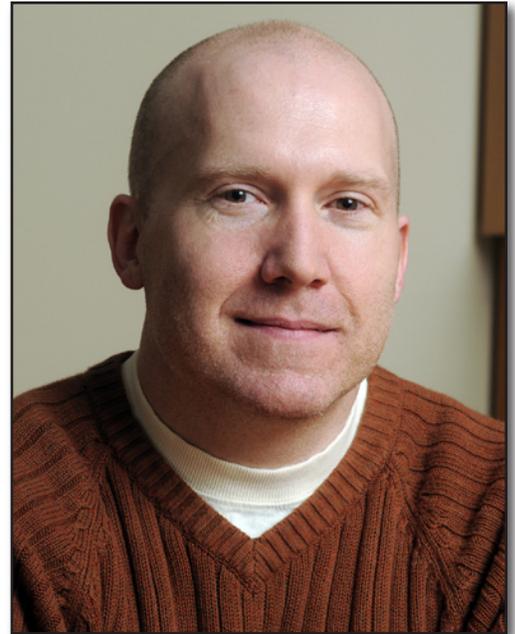
Another emphasis this time around, according to Jirles, is reaching people who don’t have access to the Internet at home, reaching them instead through schools, community organizations, workplaces, libraries, senior centers, hospitals and other central locations. Also employed was the social networking site Twitter, which those without home computers can access through cell phones.

Initial feedback from lower-income communities shows efforts to reach them have improved with the 2020 initiative, according to Jirles.

Helping announce Healthy People 2020 at the Dec. 2 gathering at The George Washington University School of Public Health and Health Services was HHS Assistant Secretary for Health [Howard Koh, M.D.](#), who called Healthy People 2020 “a momentous effort for the next decade.”

(Matt Goad is a contract writer with the NIEHS Office of Communications and Public Liaison.)

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Jirles represented NIEHS on Healthy People 2010 and 2020. (Photo courtesy of Steve McCaw)



Koh oversees 14 core public health offices and serves as senior public health advisor to the Secretary of HHS. (Photo courtesy of HHS)

Philbert named dean at Michigan

By Eddy Ball

The University of Michigan (U-M) announced the appointment of NIEHS grantee Martin Philbert, Ph.D., as dean of the U-M School of Public Health (SPH), effective Jan. 1. Philbert, a professor of environmental health sciences at U-M who has also served as interim director of what is now known as the Risk Science Center there, was a member of the [NIEHS National Advisory Environmental Health Sciences Council](#) from 2003 to 2007 ([see story](#)).

U-M President Mary Sue Coleman, Ph.D., and Provost Phil Hanlon, Ph.D., made the announcement in a Nov. 29 [press release](#). In the announcement, Hanlon was quoted as saying, “President Coleman and I are very pleased that [Dr. Philbert](#) is assuming this vital leadership role in the School of Public Health. We are confident that he will provide impressive leadership for the School of Public Health, strengthening an already excellent school.”

Looking ahead to his new role at U-M, Philbert praised his colleagues, the students, and the staff at SPH. “Together, we will work on difficult issues, develop and share solutions to common problems in public health, and implement common-sense sustainable interventions here and abroad ... to address the persistent and thorny problems affecting the health of human populations everywhere,” he said, echoing the very goals he also articulated in his role as a member of Council.

Philbert is recognized for his expertise in neurotoxicology and experimental neuropathology and most recently for his research on nanotechnology in cancer treatment and the potential health effects of exposure to nanomaterials ([see story](#)).

During his career at U-M and, prior to 1995, at Rutgers University, he has maintained a continuous federally funded portfolio of basic research activities. Philbert is a principal investigator on current projects funded by grants from the NIH, the U.S. Air Force, W.M. Keck Foundation, and National Cancer Institute. NIEHS funds two of Philbert’s grants — [Modulation of Immune-GI Function by NanoAg](#) and [Role of Astrocyte Injury in Neuroprotection](#).

During his tenure as Council member, Philbert provided advice and oversight during the administrations of three NIEHS directors — Kenneth Olden, Ph.D., who retired in 2005; David Schwartz, M.D.; and Samuel Wilson, M.D., who was named acting director in August 2007.

Philbert was often candid, but always gracious and witty at Council meetings. His final words to his colleagues reflected his dedication to helping NIEHS fulfill a mission he holds as almost sacred. He said of service as a member of Council, “It’s an opportunity here to sell the mission, to sell the work that you do and its importance to the American people. Use that time wisely.”

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During his tenure on Council, Philbert was never reluctant to speak out to protect and promote public health. (Photo courtesy of Peter Smith)

Science Notebook

Birnbaum presents Whittenberger Symposium keynote lecture

By Eddy Ball

NIEHS/NTP Director Linda Birnbaum, Ph.D., added yet another laurel to her long list of honors, when she presented the keynote talk at the 13th James L. Whittenberger Symposium Dec. 17 at the Harvard University School of Public Health (HSPH). Introduced by NIEHS grantee Douglas Dockery, Sc.D., Birnbaum delivered a lecture on “Continuing Vulnerability: Adolescence and the Reproductive Years.”

Held each year to honor the contributions of former Harvard University Professor James Whittenberger, M.D., to the field of environmental health, the seminars are sponsored by the Department of Environmental Health and the Harvard NIEHS Center for Environmental Health at the Harvard School of Public Health. Until his retirement in 1982, for 36 years, Whittenberger served the HSPH in a variety of capacities, including as founder and director of the Harvard NIEHS Center for Environmental Health.



Birnbaum has spent much of her two years as director representing NIEHS at conferences, symposia, community meetings, and congressional hearings. (Photo courtesy of Steve McCaw)

Continuing Vulnerability

Like the 12 previous Whittenberger lecturers ([see text box](#)), Birnbaum addressed an emerging and important topic in the field of environmental public health. She pointed to several diseases and conditions that have increased over the past 40 years, including testicular cancer, birth defects, some childhood cancers, asthma, difficulty conceiving and maintaining pregnancy, prematurity, pre-eclampsia, gestational diabetes, autism, and attention deficit hyperactivity disorder.

Emphasizing the importance of the total environment in the rising incidence of these diseases, Birnbaum said, “We know the human genome hasn’t changed over that time, so a genetic cause is unlikely.” However, she noted, environmental factors — chemicals, diet and nutrition, drugs, stress, climate, infections, and other factors — have changed dramatically over the past decades.

As with exposure to developmental stressors during gestation and childhood, Birnbaum continued, exposures during the sensitive adolescent and reproductive periods can trigger epigenetic alterations that lead to disease, as people move into middle life and later life. “During development, environmental stressors cause functional changes, such as altered gene expression, altered protein activity, and/or altered number of cells,” she explained, “and these functional changes persist after the environmental stress is gone.”

From the role epigenetic marks play in later development of disease, Birnbaum moved into several other areas where NIH and NIEHS research has started to shed light on disease progression through gene and environment interactions. Noting the involvement of three important chemical classes — phenols, phthalates, and phytoestrogens — in the decreasing age of puberty, Birnbaum connected them with increases in body mass index and the rate of breast and pubic hair development.

Birnbaum also noted studies of glucocorticoid receptor (GR) gene expression that have provided insights into the long-term effects of maternal behavior on offspring. “From studies looking at GR methylation and suicide,” she said, “we see a clear connection to a history of childhood abuse, and specific effects in certain areas of the brain of suicide victims.”

After discussing epigenetics and asthma, Birnbaum turned to NIEHS- and NIH-funded research programs on neurodevelopment and breast cancer — complex diseases influenced by a matrix of environmental exposures, such as chemical exposure, diet, and ionizing radiation, during sensitive periods of development. She concluded by reinforcing the central concepts that are the foundation for the gene-environment interaction paradigm to explain the increase of disease.

Previous lectures in the James L. Whittenberger Symposium series

1984 Norton Nelson, Ph.D., “Airborne Particles: Poisons, Probes, and Prophylactics”

1986 Ian Higgins, M.D., “Environmental Epidemiology: Dose Response”

1987 Bernard Goldstein, M.D., “Topics in Ozone Toxicity”

1988 David Bates, M.D., “Ozone – Myth and Reality”

1989 Margaret Becklake, M.D., “Industrialization: A Challenge to the Lung”

1992 John M. Peters, M.D., “Environmental Factors and Childhood Leukemia”

1994 Symposium on Respiratory Physiology and Environmental Health in Honor of James L. Whittenberger’s 80th Birthday

1997 Jonathan Samet, M.D., “Radon”

1999 Scott Weiss, M.D., “The Asthma Epidemic: Is It Due to Genes, the Environment, or Both?”

2007 David Schwartz, M.D., “Epigenetics and Environmental Asthma”

2008 David Barker, M.D., Ph.D., “Nutrition in the Womb: The Origins of Chronic Disease”

2009 Philip J. Landrigan, M.D., “The Unique Vulnerability of the Developing Human Brain to Toxic Chemicals in the Environment”

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Aston-Jones explores the biology of addiction

By Negin Martin

Neurobiologist Gary Aston-Jones Ph.D., discussed the role of orexin neurons in reward-seeking behavior and addiction in his 2010-2011 Distinguished Lecture Series presentation at NIEHS Nov. 23, "Seeking Rewards: Overdoing It With Orexin Neurons."

Findings by the Aston-Jones laboratory suggest a novel role for orexin in promoting addictive behavior and drug relapse, as well as its involvement in learning and synaptic plasticity. According to Ashton-Jones, chemical manipulation of these neurons may offer a new therapeutic avenue for reprogramming the drug-seeking response, as orexin analogs show pharmacological potential in modifying behavior.

Aston-Jones holds the Murray Chair of Excellence in Neuroscience and is the director of the Center for Cognitive Neuroscience at the Medical University of South Carolina. Research in his lab has unraveled chemical pathways and neurophysiological circuitries responsible for cognitive performance and acquisition of reward-stimulus association.

Aston-Jones' contributions to the field have deepened understanding of the neuromodulatory signals that underlie mammalian behavior and learning. During his lecture at NIEHS, Aston-Jones shared his latest findings about the function and mechanisms of orexin neurons in the reward system, animal responses in Pavlovian and instrumental drug-seeking experiments, and the mapping of additional areas in the brain affected by addiction.

Orexin neurons connect with many parts of the brain

Orexin neurons are exclusively located in the hypothalamus. Despite their small number, these neurons have widespread projections to the cerebral cortex, midbrain, and the spinal cord that position them as key regulators of neurotransmission.

Release of the neuropeptide orexin is generally thought to be involved in arousal, stimulating food and drug intake and maintenance of the waking state. Conversely, mutations in orexin receptors OXR1 and OXR2 have been associated with narcolepsy and cataplexy, a partial or complete loss of muscle tone, in experiments with dogs and rodents.



Aston-Jones' work has been funded by the National Institute on Drug Abuse and Lilly Pharmaceuticals. His research has clear potential in the development of drugs to treat people with a range of addictions, along with adding to the understanding of the interplay of biology and environment in learning. (Photo courtesy of Steve McCaw)



Among NIEHS scientist drawn to the talk was Jau-Shyong Hong, Ph.D., right whose Parkinson's research also explores the role the neurotransmitter dopamine plays in brain function. (Photo courtesy of Steve McCaw)

Orexin aids memory of morphine and cocaine pleasure

The ventral tegmental area (VTA) in the brain manages learning and the formation of stimuli-reward associations innervated by orexin neurons. Using Fos expression in the brains of test animals as an indicator for neuronal activity during cocaine preference, researchers discovered that orexin neurons are activated by reward-associated stimuli.

One of the behavioral assays commonly used in neurobiology to study addictive behavior in rodents is the conditioned place preference (CPP) paradigm. With CPP on drug-free test days, researchers can measure the degree of preference for a stimulus associated with a reward in response to context-induced environmental cues. Assessing behavioral response in rodents, researchers demonstrated that orexin neurons are stimulated during conditioning for learned preferences for stimuli associated with rewards such as morphine, cocaine, and food. In turn, chemical inhibition or stimulation of orexin neurons significantly affected reward-associated behavior in rats during CPP testing.

Dopamine neurons get a boost from orexin

Mood, attention, and memory are all influenced by the function of dopamine neurons. Long-lasting increases in neurotransmission, known as long-term potentiation or LTP, strengthen synaptic connections and affect plasticity.

Changes in synaptic connections and their strengths in VTA dopamine neurons are implicated in drug-related behavior. Each repeated cocaine use, for example, induces a larger LTP in dopamine neurons, strengthening neuronal connections associated with the drug reward.

Orexin neuron projections into the VTA region directly influence LTP in the VTA dopamine neurons. Local administration of orexin enhances the VTA dopamine neuron response to stimulation. Consistent with this result, disruption of orexin input results in extinguished addictive behavior in rodents.

Orexin regulation of dopamine neuron plasticity is complicated by the factors such as the type and source of the stimulation, which directly modulate function of the neurons in the circuitry.

(Negin Martin, Ph.D., is a biologist in the NIEHS Laboratory of Neurobiology Viral Vector Core.)



The Distinguished Lecture Series also attracts specialists in other fields, such as NIEHS Principal Investigator and Chief of Laboratory of Reproductive and Developmental Toxicology Ken Korach, Ph.D., whose principal research interest is the stimulation of estrogenic response. (Photo courtesy of Steve McCaw)



Host Patricia Jenson, Ph.D., the principal investigator of the NIEHS Developmental Neurobiology Group in the Laboratory of Neurobiology, joined Ashton-Jones for the question and answer session. She said of his research, "This work has really laid the foundation for many researchers to follow in studying the system, including the work in my own lab." (Photo courtesy of Steve McCaw)

Novel small RNA molecules regulate stem cell self-renewal

By L.H. Lazarus

Yale University School of Medicine researcher Haifan Lin, Ph.D., visited NIEHS recently to talk about exciting new discoveries he has made with stem cells. His presentation discussed the epigenetic regulation of stem cells by novel small RNA molecules and included information on the involvement of stem cells in diseases such as testicular and intestinal cancer. Laboratory of Molecular Carcinogenesis Principal Investigator Guang Hu, Ph.D., hosted the Dec. 14 seminar as part of the NIEHS Distinguished Lecture Series.

Lin, director of the Yale Stem Cell Center and professor of Cell Biology and Genetics, began with an overview of his discovery of the Argonaute (AGO)/PIWI family of proteins. He stated, “This family contains highly conserved sequences that exist throughout evolution in both animal and plant kingdoms. The *ago/piwi* family of genes represents the only known genes required for stem cell regulation.”

According to Hu, the impact of Lin’s work “greatly enhanced our understanding about adult stem cell maintenance and self-renewal, and will contribute to the development of stem cell therapies and regenerative medicine using adult stem cells.” Lin’s presentation, he continued, “was very inspirational to me and people in my group.”



In addition to his many honors, Lin was also a recipient of the 2010 NIH Director’s Pioneer Award for conducting innovative and groundbreaking research. (Photo courtesy of Steve McCaw)

Using fly and mouse cells to study cancer

Lin uses *Drosophila* and mouse model systems to explore the asymmetric division of stem cell self-renewal. His research determined that over-proliferation of stem cells leads to cancer, while under-proliferation leads to tissue dystrophy, anemia, immunodeficiency, or infertility.

An important attribute of the AGO/PIWI proteins is their ability to bind to a class of non-coding small RNA molecules, termed PIWI-interacting RNAs (piRNAs). piRNAs consist of a class of small regulatory RNAs, which are slightly larger than other known classes of regulatory RNAs.

Lin summarized four salient features of piRNAs:

- More than 60,000 species exist.
- They lack sequence consensus, except for partial homogeneity at the 5’ terminus.
- They are derived from selective loci on chromosome 17 in mice and may be transcribed from a single precursor RNA.
- They are associated with intergenetic repetitive sequences in genes and transposons, DNA sequences that move to new positions within the genome.



The presentation inspired a question from NIEHS Principal Investigator Mike Resnick, Ph.D., head of the Chromosome Stability Group. (Photo courtesy of Steve McCaw)

Evidence for the PIWI-piRNA complex

The determinant factor for epigenetic regulation by piRNAs relies on its binding to the amino acid sequence in PIWI, Lin explained. Site-specific mutation analysis of PIWI and its molecular docking with piRNA verified its role in the development of stem cells in testis germinal epithelium.

Lin stressed that PIWI-piRNA complexes and related proteins play central roles in biological systems ranging from the fruit fly *Drosophila* to humans. He continued, “The PIWI-piRNA complex is the key component that interacts with canonical components in genetics.”

Early studies demonstrated that overexpression of PIWI increased the number of egg chambers in *Drosophila* ovaries. A comparable study using testicular tissue with HIWI, the human analog, revealed a correlation between overexpression of HIWI and cancer of the germinal epithelium of the testis, also known as seminomas.

Lin also talked about HIWI’s involvement in intestinal cancer. While HIWI is found in stem cells in normal gastric mucosa, its over-expression leads to ectopic gastric cancers, such as atrophic gastritis and intestinal metaplasia. Lin reiterated, “Reducing HIWI inhibits the formation of cancer.”



Hu, right, shown moderating the question and answer session, found Lin’s research applicable to his interests. Hu added, “We study self-renewal in embryonic stem cells, and we could apply similar approaches Dr. Lin pioneered in his work.” (Photo courtesy of Steve McCaw)



Christina Teng, Ph.D., above, is a molecular biologist in the NTP Biomolecular Screening Branch. (Photo courtesy of Steve McCaw)

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Guest lecture underscores environmental links to autism

By Thaddeus Schug

Environmental factors are likely among several contributors to the rapid rise in new cases of autism seen in California and throughout the nation, according to guest lecturer Irva Hertz-Picciotto, Ph.D., an epidemiologist and [NIEHS grantee](#) at the University of California (UC), Davis.

[Hertz-Picciotto](#) reported these findings Dec. 6 in a seminar titled, “An Update on Environment and Autism: Findings from the CHARGE [Childhood Autism Risks from Genetics and Environment] Study,” as part of

the Keystone Science Lecture Seminar Series at NIEHS. Hertz-Picciotto is chief of the division of environmental and occupational health at UC Davis, and principal investigator of the NIEHS-funded study.

The combination of changes in diagnostic criteria, increased parental awareness, and environmental risk factors, has led to an eight-fold increase in cases of autism in the past ten years, she explained.

Gene and environment interaction

The NIEHS-funded CHARGE Study began in 2003 as one of the projects in the UC Davis Center for Children’s Environmental Health and Disease Prevention. The study has examined 1,400 children with differing patterns of development. The goal of the program is to better understand the causes and contributing factors for autism or developmental delay.

Three groups of children are currently enrolled in the CHARGE study: children with autism, children with developmental delay who do not have autism, and children from the general population. All of them are evaluated for a broad array of exposures and genetic susceptibilities.

Many researchers believe the continuous increase in autism cases over the last decade can be explained solely by artifacts, such as the recent broadening of the diagnostic criteria. “These artifacts do explain part of the rise in autism cases, but they don’t account for the majority of the trends we are witnessing,” said Hertz-Picciotto.

Hertz-Picciotto explained that evidence gathered from studies of monozygotic (identical) twins and the rubella epidemic in the late 1960’s revealed that congenital exposure is associated with incidence rates of autism. “Environmental factors are not limited to just chemical exposure. We need to account for the physical, social, and developmental world of children,” added Hertz-Picciotto.

The complexities of autism

“It is becoming more and more evident that multiple environmental and genetic factors contribute to elevated risks of autism, and the challenge is identifying these associations,” said Hertz-Picciotto. “I don’t believe that just one gene or one exposure can account for all cases of autism — it is much more complicated than that,” she noted ([see related story](#)).



Hertz-Picciotto called for more research into the environmental causes of autism. In addition to the CHARGE Study, she and colleagues at UCD are participating in the NIEHS-sponsored Early Autism Risk Longitudinal Investigation (EARLI) and the Markers for Autism Risk in Babies — Learning Early Signs (MARBLES) programs. (Photo courtesy of Steve McCaw)



Shown, left to right, NIEHS intramural program scientists Stephanie London, M.D., Dr.P.H., Matthew Longnecker, M.D., Sc.D., and Windy Boyd, Ph.D., listened attentively during the seminar. (Photo courtesy of Steve McCaw)

“The CHARGE study was designed to cast a very broad net to try to capture potential gene-environmental factors associated with the risks of autism,” said Hertz-Picciotto. She pointed to a case in which her group examined the autism rates associated with maternal supplementation and genes associated with one carbon metabolism. “What we found was that children with certain genetic polymorphisms, born to mothers who supplemented their diet with folic acid, had much lower incidences of autism.”

Hertz-Picciotto concluded the seminar saying, “A lot has changed in the environment over the last 10 to 15 years, especially our exposure to chemicals in our food and in our homes.” She pointed out that dozens of chemicals in the environment are neurodevelopmental toxins, which means they alter how the brain grows. “Mercury, polychlorinated biphenyls, lead, brominated flame retardants, and pesticides are just a few potential culprits that we need to study in more detail,” she added.

“Irva’s work illustrates the enormous complexities and challenges found in autism research,” said Cindy Lawler, Ph.D., a program administrator in the NIEHS Division of Extramural Research and Training, and organizer of the lecture. Lawler added, “Clearly, more and more evidence is emerging that implicates the role of gene-environment interactions in the etiology of autism.”

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

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NIEHS toxicologist Jean Harry, Ph.D., whose research involves toxic exposure to the brain and nervous system, questioned Hertz-Picciotto about her studies involving mercury exposure and autism risks. (Photo courtesy of Steve McCaw)



Lecture host Cindy Lawler, Ph.D., left, and colleague Kim Gray, Ph.D., have both overseen grants supporting Hertz-Picciotto’s research. (Photo courtesy of Steve McCaw)

Crouch links RNase H to infectious and genetic diseases

By Jeffrey Stumpf

A presentation by guest lecturer Robert Crouch, Ph.D. provided insight into an RNA cleaving enzyme, whose production he playfully called “the purpose in life.” His talk at NIEHS Dec. 10 described cleavage of RNA/DNA hybrids by Ribonuclease H (RNase H), its importance to human health, and its potential applications in the treatment of genetic and environmental disease.

Crouch is the head of the [Section on Formation of RNA](#) at the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD). His talk was the latest in the Laboratory of Molecular Genetics (LMG) Fellows Invited Lecture Series and was hosted by postdoctoral fellow Danielle Watt, Ph.D., a member of the DNA Replication Fidelity Group.

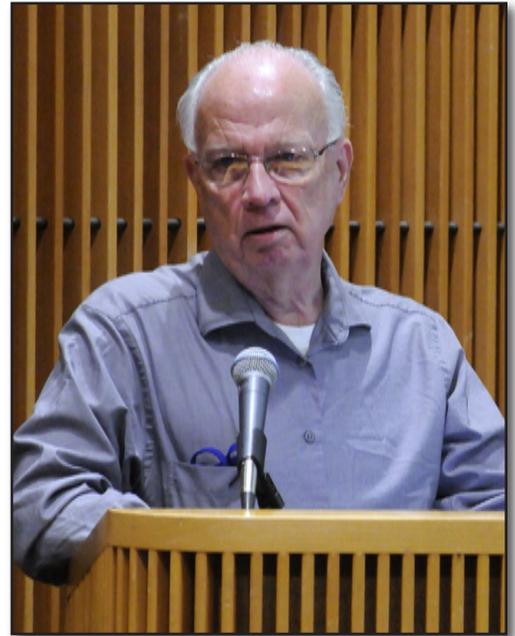
Crouch’s talk reviewed both RNase H1 and H2 in archeobacteria, *E. coli*, yeast, mouse, and humans. The two enzymes differ by their substrate preference, determined by the number and location of ribonucleotides in the RNA component of the RNA/DNA hybrid.

An example of a natural RNA/DNA hybrid substrate occurs in the beginning of transcription. RNA is produced but still annealed to the template DNA, forming bubbles called R-loops that lead to genomic instability. Overexpressing RNase H1 can reduce the instability caused by R-loops. However, these R-loops may be a key intermediate in promoting the variety of antibodies needed for the immune system. Therefore, the RNase H expression may be regulated differently depending on the location of the R-loop.

Loss of RNase H1 leads to mitochondrial DNA depletion

Eliminating RNase H1 caused embryonic lethality in mice. Surprisingly, development is aborted because of the lack of mitochondria DNA (mtDNA) replication. Unlike other genes necessary for mtDNA replication, mutations in RNase H1 have not been identified in mitochondrial disease patients. NIEHS mtDNA researcher [William Copeland, Ph.D.](#), suggested, “The embryonic lethality and loss of mtDNA in the mouse knockout makes RNase H1 a good candidate for mitochondrial disease-associated mutations, despite its dual role in the nucleus.”

Crouch showed two distinct forms of RNase H1 that differed by the presence of a mitochondrial targeting sequence at the beginning. The ratio of mitochondrial to nuclear RNase H1 may fluctuate in different cell types. “It is not yet clear that some cells need both forms,” Crouch said. “Cells that are non-dividing may need mtDNA replication but not need the nuclear enzyme.”



Like most guest speakers in the series, Crouch said he was especially honored to be invited by the fellows. (Photo courtesy of Steve McCaw)



Principal Investigator Thomas Kunkel, Ph.D., was one of several scientists who asked questions following the lecture. Like Kunkel himself, Crouch works at the intersection of molecular genetics and structural biology. (Photo courtesy of Steve McCaw)

Linking active site biochemistry to treatments of HIV infection and genetic diseases

Detailed studies by Crouch of the active site of RNase H are extremely relevant to two major health-related topics:

- RNase H of HIV virus is required for production of infectious particles.
- Mutations in RNase H2 associate with Acardi Goutières Syndrome (AGS), a rare but fatal disease that mimics *in utero* viral infection.

HIV RNase H has yet to be successfully targeted for treating HIV/AIDS, but as Crouch pointed out, understanding the active site structure and function may aid this approach.

“So far all of these small molecule inhibitors have failed either because they do not enter cells or because the active site of RNase H is inaccessible to the drug,” added Crouch. “The active site is almost always occluded by the presence of the viral RNA or replication intermediates.”

The 28 known mutations in human RNase H2 that associate with AGS are located in every region of the gene. The mutations located in the active site likely inhibit cleavage of or accessibility to the RNA/DNA hybrid. Mutations far from the catalytic domain may affect protein stability or interactions with unknown cofactors.

But how does RNase H2 play an essential role in what appears to be an immune disease? The answer, Crouch suggested, may help scientists understand how the immune system responds to different types of DNA.

“RNase H2 may insure that some substrates do not elicit the innate immune response,” Crouch explained. “In some cases, RNase H2 may have a role in protection from viruses or other detrimental nucleic acids.”

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

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The talk appealed to a range of scientists at NIEHS, including Nuclear Magnetic Resonance Group Center Manager Eugene DeRose, Ph.D., left, and Principal Investigator Bob London, Ph.D. (Photo courtesy of Steve McCaw)



Watt watched as several scientists took advantage of the question-and-answer session. She represented LMG trainees in hosting Dr. Crouch's presentation. (Photo courtesy of Steve McCaw)

Study proposes new paradigm for the field of environmental toxicology

By Eddy Ball

A new NIEHS-funded paper offers insight into how organic pollutants impact the delivery of therapeutic drugs to the central nervous system (CNS). The findings, the authors maintain, are the first of their kind and suggest a new paradigm for the field of environmental toxicology centered on the role of the aryl hydrocarbon receptor (AhR) in targeting the blood-brain barrier in mammals.

The [study](#) is the latest publication by scientists in the NIEHS Intracellular Regulation Group headed by Principal Investigator and Acting Scientific Director [David Miller, Ph.D.](#), which has explored the mechanisms that regulate blood-to-brain transport ([see story](#)). First author on this latest study by the group is Research Fellow [Xueqian \(Shirley\) Wang, Ph.D.](#) Former postdoctoral fellow Brian Hawkins, Ph.D., is also a coauthor on the paper.

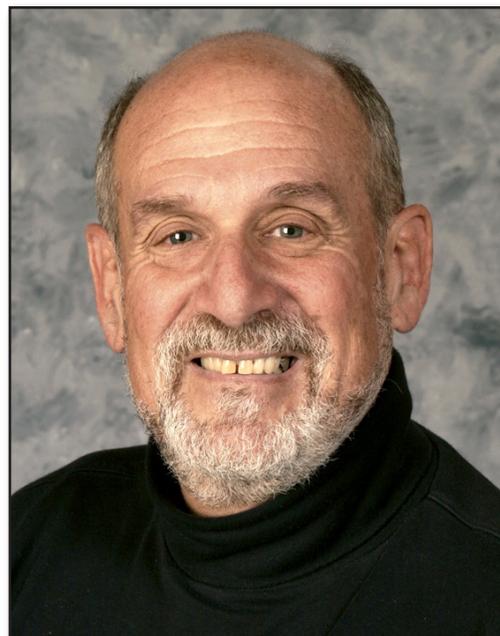
Tightening the blood-brain barrier in response to environmental exposure

As the authors explain in their introduction to the study, only recently has research suggested that AhR activation could increase production of proteins known as ABC transporters.

These transporters are major determinants of uptake, distribution, and excretion of foreign chemicals in the body. In the brain capillary endothelium, which comprises the blood-brain barrier, ABC transporters restrict entry of neurotoxicants into the brain and are thus neuroprotective. However, at the same time, they limit transport of therapeutic drugs into the central nervous system. The study shows that AhR activation increases ABC transporter expression, thus decreasing drug delivery to the brain.

The new study takes our understanding of blood-brain barrier regulation a major step forward by demonstrating *in vitro*, and more importantly *in vivo*, the effects of exposing rat brain capillaries to very low levels of the dioxin, TCDD, a widespread environmental pollutant and potent activator of AhR.

This level of exposure, the scientists found, activates AhR and increases the expression and transport activity of the ABC transporter, P-glycoprotein. These findings establish the blood-brain barrier as a dioxin target tissue.



As Miller demonstrated in a 2010 paper, the blood-brain barrier may also play a role in Alzheimer's disease — by blocking the elimination of amyloid beta protein from the brain ([see story](#)). (Photo courtesy of Steve McCaw)



Wang received awards this year from the [Society of Toxicology](#) and [NIH](#) for her research on the role of AhR in blood-brain barrier function. (Photo courtesy of Steve McCaw)

Implications for drug delivery, toxicology, and public health

The researchers speculate that other dioxins, dioxin-like polychlorinated biphenyls (PCBs), and many polycyclic aromatic hydrocarbons may act in a similar way to alter barrier function. They suggest that a better understanding of how chemicals that activate AhR alter blood-brain barrier function may provide insight into patient-to-patient variability in response to CNS-acting drugs.

By elucidating the mechanisms of AhR activation of ABC transporters at the blood-brain barrier, the team has contributed to our understanding of the mode of action of dioxin.

Citation: Wang X, Hawkins BT, Miller DS. 2010. Aryl hydrocarbon receptor-mediated up-regulation of ATP-driven xenobiotic efflux transporters at the blood-brain barrier. *FASEB J.* 25. Epub ahead of print. doi: 10.1096/fj.10-169227

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Hawkins is currently a researcher in the Department of Hematology at the University of Washington School of Medicine. (Photo courtesy of Steve McCaw)

Chatterjee wins Young Investigator Award

By Sophie Bolick

Saurabh Chatterjee, Ph.D., a visiting fellow with the NIEHS Free Radical Metabolism Group, was awarded the prestigious Young Investigator Award at the Annual Meeting of the Society for Free Radical Biology and Medicine (SFRBM).

Held this year Nov. 16-20 in Atlanta, the SFRBM annual meeting is the largest of its kind for researchers working in the field of free radical biology and medicine, drawing approximately 750 scientists from all over the world. The Young Investigator Award recognizes the best scientific presentation as determined by a panel of judges.

Liver toxicity associated with environmental exposure

How obesity potentiates environmental hepatotoxicity has been the focus of Chatterjee's research at NIEHS. According to Chatterjee, many chemicals used at low doses do not have any visible health effects in normal, healthy adults. However, in obese individuals, there are health effects, thought to occur, in part, through free radical formation. Approximately 20 percent of obese Americans have liver problems, which may be associated with free radical formation.

Chatterjee is studying the effects of bromodichloromethane, a water disinfection byproduct formed when chlorine is used to treat swimming pools and tap water, on mice. Normal, healthy mice are unaffected by low doses of this chemical, while diet-induced diabetic mice develop steatohepatitis, or liver inflammation. He is studying the mechanisms by which this occurs, as well as the role of leptin, a proinflammatory adipocytokine, in this process. "This is an important area of research because liver inflammation can lead to more serious diseases like autoimmune hepatitis and liver cirrhosis," said Chatterjee.

Award recognizes work of young scientists

According to Free Radical Metabolism Group chief Ron Mason, Ph.D., winning the Young Investigator Award is a great recognition for young scientists, with some previous awardees from the group, including Marcelo Bonini, Ph.D., going on to highly successful careers in academia. Chatterjee would like to transition from NIEHS to an independent investigator position, continuing his research on the effects of environmental toxicants in obesity-induced inflammation.

Chatterjee credits his fellowship at NIEHS for giving his career “a huge boost, especially under the mentorship of Dr. Mason.” He continued, “I have a high degree of freedom to develop independent ideas and put them in research perspective.” He also acknowledged the resources offered by the Office of Fellows’ Career Development, headed by Diane Klotz, Ph.D., as being an immense help. Workshops focusing on the various aspects of career development and grantsmanship have proven invaluable to his growth as a scientist.

Chatterjee, a native of India, was drawn to NIEHS by the highly regarded work done by the Free Radical Metabolism Group. He considers Mason’s group to be “one of the most renowned labs in the country for free radical biology.” Chatterjee received his M.S. in Human Physiology and worked as an assistant scientist at the Radiation Biology and Health Sciences Division of the Government of India Department of Atomic Energy while earning his Ph.D. at the University of Mumbai. With a background in immunotoxicology, he focused his research on radiation-related effects on biological systems, including inflammation and heat stroke.

(Sophie Bolick, Ph.D., is a postdoctoral fellow with the Molecular and Genetic Epidemiology Group in the Laboratory of Molecular Carcinogenesis.)

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Highlighting the role of nutrition in host susceptibility

By Eddy Ball

The old adage about an apple a day keeping the doctor away picked up a Superfund Research Program (SRP) twist during a half-day workshop Dec. 2 at the University of Kentucky (UK). With an impressive lineup of speakers that included NIEHS SRP Director Bill Suk, Ph.D., the workshop explored the topic “Nutrition, Superfund Chemical Toxicity, and Risk Assessment.”

In his opening comments, Suk commended organizers of the [UK SRP](#) workshop on their choice of topics. “Environmental insult can never be isolated from the way an individual host will respond to it,” he said. “It’s clear that nutrition can be a potential modulator of diseases that have been associated with exposure to environmental stressors, and this interplay will have important implications in risk assessment.”



Chatterjee has been very successful while at NIEHS, publishing peer-reviewed publications, as either a first or contributing author. He was also a winner of a Fellows Awards for Research Excellence in 2008 and again this year. (Photo courtesy of Saurabh Chatterjee)

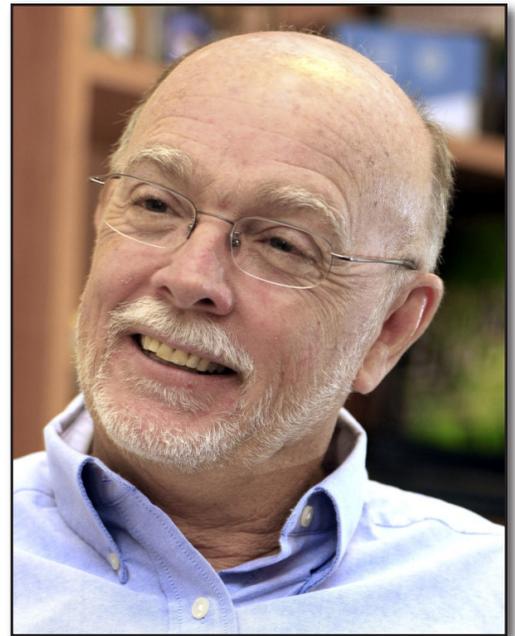
Developing this theme were researchers from several universities and the U.S. Environmental Protection Agency (EPA), an SRP partner. The workshop was divided into two sessions — one exploring the interaction of nutrition and environmental exposure, and the other surveying the ramifications for risk assessment and study design.

The first speaker, Craig McClain, M.D., offered a clinical perspective on diet and liver disease with his presentation on “Nutrition, Toxins and Steatohepatitis.” He was followed by speakers who surveyed nutritional factors that help protect the host — “Polyunsaturated Fatty Acids (PUFA), Environmental Pollutants and Endocannabinoids,” by Bruce Watkins, Ph.D. — and ones that may amplify dose response and make the host more susceptible — “Chemical Obesogens and the Obesity Epidemic,” by Bruce Blumberg, Ph.D.

EPA representatives explored the regulatory implications of nutritional modulation of the impact of environmental exposures. Annette Gatchett, acting director of the Cincinnati Division of EPA’s National Center for Environmental Assessment (NCEA), pondered the difficulties her group faces in a talk titled “Decisions, Decisions: Complexities of Multiple Stressors in Human Health Assessments.” With a reference to the father of his field, NCEA toxicologist Jason Lambert, Ph.D., examined diet as a regulator of dose response in his talk, “Paracelsus Tempered: Nutrition as a Biological Rheostat in Cumulative Mixtures Risk Assessment.”

The final talk of the day tied together the two sections of the workshop, as Wayne Sanderson, Ph.D., outlined the challenges for future research, “Nutrition: The Over Looked Confounder and Effect Modifier in Occupational and Environmental Disease Studies.” Whether investigators are looking at endocrine disruptors or particulate air pollution, they need to understand that an important part of people is what people eat, and nutrition may well hold the key to why some people are acutely susceptible to environmental exposures, while others seem be unaffected.

Bernhard Hennig, PhD, director of the UK SRP, gave closing remarks, thanking presenters and challenging the audience to explore the nutritional paradigm. “Nutritional interventions may provide the most sensible means to develop primary prevention strategies of diseases associated with many environmental toxic insults,” he concluded.



Suk above, told the audience that growing awareness of what is known as the exposome — the sum total of what makes up the host’s internal environment — is changing the scope of toxicology and risk assessment. (Photo courtesy of Steve McCaw)



The speakers gathered at the end of the workshop. Shown, left to right, are Gatchett, Blumberg, Hennig, McClain, Sanderson, Watkins, Suk, and Lambert. (Photo courtesy of UK SRP)

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Miller presents study on erionite exposure and mesothelioma

By Matt Goad

In Cappadocia, Turkey, it is too late for generations of victims of mesothelioma in so-called cancer villages, where up to half of the villagers die from the rare lung cancer. But a collaborative program in the United States, including work by NIEHS Senior Medical Adviser [Aubrey Miller, M.D.](#), may be able to save lives here before the problem of erionite exposure has the same effect.

Miller presented a study that compared levels of erionite, a mineral fiber similar to asbestos, and perhaps even a more potent carcinogen, in Dunn County, N.D., and the Turkish villages. Miller co-authored the study with Michele Carbone, M.D., Ph.D., director of the University of Hawaii Cancer Center. They presented the results of the [study](#) Dec. 9 at the [Chicago Multidisciplinary Symposium in Thoracic Oncology](#) ([view slides](#)).

Contaminated school bus routes

According to Miller, gravel that is contaminated with erionite is the only gravel readily available in Dunn County, N.D., and, over the past two to three decades, about 300 miles of road have been paved with erionite gravel, including more than 30 miles of school bus routes. The comparison with Turkey showed that levels of erionite in the air equaled and even exceeded levels measured in the town of Boyali, where 6.2 percent of all deaths are caused by mesothelioma, but were generally lower than those found in Turkish villages where mesothelioma-related deaths ranged from 20 to 50 percent of all deaths. Miller said researchers also found in North Dakota that people riding bicycles or riding inside of cars and school buses driving on the gravel roads could be exposed to markedly elevated airborne levels of erionite.

“This is a continuing project,” Miller said. “There have been a number of questions about what are we going to do from a public health perspective, so the first element was to understand the exposures and characterize the exposures here in the United States, at least in North Dakota.”

No current regulations

Erionite is not regulated in the United States, but federal, state, and local agencies are working to reduce current use of erionite, with an eye toward dealing with the erionite gravel already in place. Erionite deposits are present in several U.S. states, including California, Oregon, North and South Dakota, Arizona, and Nevada.

There is a latency period for mesothelioma of up to 50 years, Carbone said, so the dangers of erionite may have been discovered in time to greatly reduce the risks in the U.S. No spike in mesothelioma-related deaths has yet been identified in North Dakota. However, a recent radiographic [study](#) by researchers from the University of Cincinnati identified bilateral pleural plaques in two of 15 road workers with no history of asbestos exposure.

Also involved in various aspects of the study have been researchers from Hacettepe University in Ankara, Turkey; the Department of Geophysical Sciences at the University of Chicago; the Department of Chemical and Biochemical Engineering at the University of Iowa; the Department of Environmental Health at the University



The erionite study is an outgrowth of Miller's work with asbestos contamination in Libby, Mont., which he discussed during a [talk](#) at NIEHS last year. (Photo courtesy of Steve McCaw)

of Cincinnati; the Centers for Disease Control and Prevention Agency for Toxic Substances and Disease Registry; the U.S. Geological Survey; and the U.S. Environmental Protection Agency, Denver office.

(Matt Goad is a contract writer with the NIEHS Office of Communications and Public Liaison.)

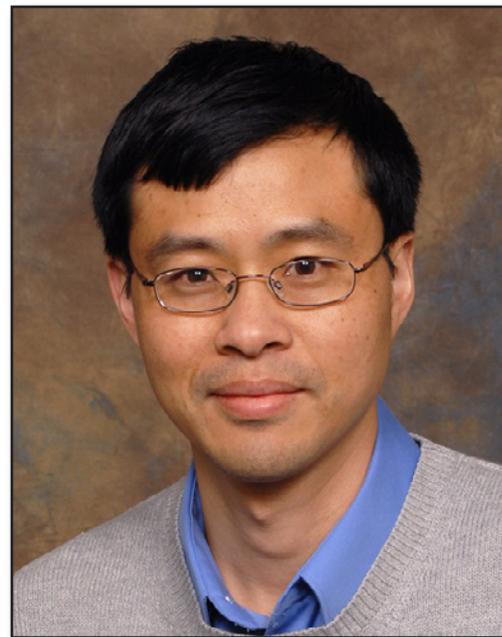
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Review emphasizes potential dangers of e-waste

By Melissa Kerr

A new NIEHS-funded analysis is sending a wake-up call on the emerging health concerns posed by electronic waste (e-waste) disposal practices worldwide that have resulted in what the researchers described as “an unprecedented mixture of exposure to heavy metals and persistent organic pollutants.”

“In developing countries where most informal and primitive e-waste recycling occurs, environmental exposure to lead, cadmium, chromium, polybrominated diphenyl ethers (PBDEs), polychlorinated biphenyls (PCBs), and polycyclic aromatic hydrocarbons (PAHs) is prevalent at high concentrations in pregnant women and young children,” they wrote. “Developmental neurotoxicity is a serious concern in these regions, but human studies of adverse effects and potential mechanisms are scarce.”



Lead author Chen is an assistant professor in the Department of Environmental Health at the UC College of Medicine with research interests in perinatal and pediatric epidemiology. (Photo courtesy of UC)

 **Linked video:**
[Watch people recycling e-waste in India \(7:51\)](#)
(Launches in new window)

Download Media Player:  Flash 

Published online in the journal Environmental Health Perspectives (EHP) and led by scientists in the Department of Environmental Health at the University of Cincinnati (UC) College of Medicine and in the Shantou University Medical College in China, the [study](#) raises important questions about regulation to address potentially widespread exposure among susceptible populations to known carcinogens and potent neurotoxicants.

NIEHS [grantee](#) and UC epidemiologist [Aimin Chen, M.D., Ph.D.](#), and co-authors reviewed articles and papers related to e-waste and the potential hazards posed by exposure to it. Their findings suggest that women who are pregnant and young children are most at risk if they live near an e-waste recycling site. In a [UC press release](#), Chen said, “Because the brain is in a state of rapid development and the blood-brain barrier in infants and young children is not as effective as in adults, neurotoxic substances, such as heavy metals, can cause developmental damage.”

Demand for electronics drives waste explosion

With the digital revolution moving forward with no signs of abating, e-waste is following the same upward trend. This explosive growth has outpaced management policy development, both in developed and developing countries. E-wastes, such as cathode ray tubes, desktops, cell phones, and copiers, are composed of several metals and chemical pollutants that have the potential to cause adverse health effects, the researchers warned.

According to the study, a significant amount of e-waste is exported to developing countries and recycled in local towns and villages using primitive technologies to recover gold, silver, zinc, iron, tin, and other metals for profit. Because of a lack of regulation of e-waste recycling in these developing countries, the workers at the waste sites, as well as the women and children who live around them, are at a risk of exposure to toxicants.

The study notes that an estimated 20–50 million tons of e-waste are produced worldwide on an annual basis. In the United States, it is estimated that 80 percent of electronics are sent to landfills where metal can leach into the soil. A small percentage is burned, producing highly toxic airborne chemicals. In 25 states, there is limited legislation regarding disposal of electronics, but there are no enforceable federal policies regulating production or disposal.

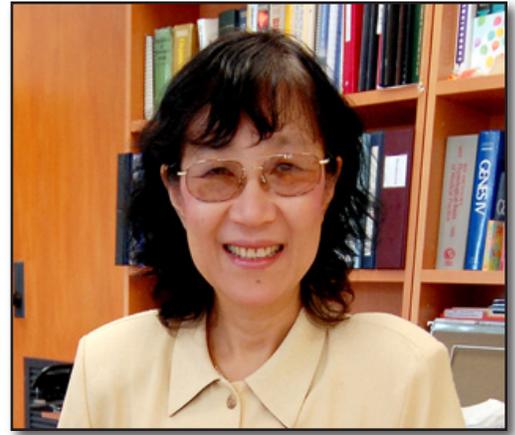
Working toward a solution

Chen's team sought to bring perspective to this growing problem. They reviewed over 120 articles and papers on the health effects of compounds found in e-waste, as well as reports published through governmental and non-governmental organizations on e-waste practices. Their study calls for continued research to fill the data gap to provide policy makers with the knowledge required for intervention plans.

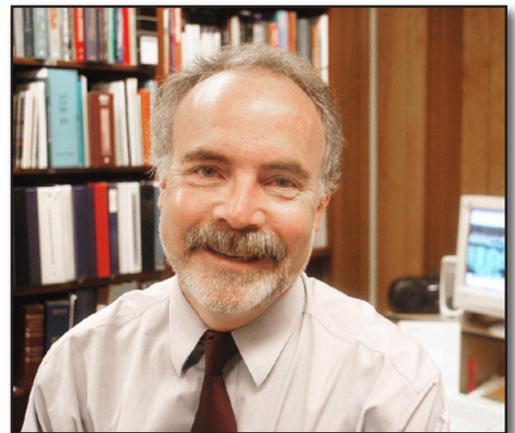
Not only does the article call for broader e-waste management, it also advocates for a preventive approach. Scientists and engineers should work on ways to restrict the amount of toxicants in the manufacturing of electronic devices through greener design and manufacturing practices, the researchers said.

“In countries where primitive recycling processes exist, human health – especially children's health – should drive regulation and management of recycling activities,” Chen explained. With the results of the study in hand, Chen hopes to bring attention to an exposure situation in immediate need of effective control.

The team's study will appear in a print edition of EHP in early 2011.



Shuk-mei Ho, Ph.D., is the chair of the Department of Environmental Health at the UC College of Medicine and principal investigator on a center grant funded by NIEHS since 1992. (Photo courtesy of UC)



A professor in the Department of Environmental Health at UC College of Medicine, co-author Kim Dietrich, Ph.D., uses a wide range of neuroassessment tools and biomarkers in his studies of lead exposure. (Photo courtesy of UC)



Co-author Xia Huo, Ph.D., is the director of the Analytical Cytology Laboratory at the Shantou University Medical College in China. (Photo courtesy of Xia Huo)

Citation: [Chen A, Dietrich KN, Huo X, Ho SM. 2010. Developmental Neurotoxicants in E-Waste: An Emerging Health Concern. Environ Health Perspect. doi:10.1289/ehp.1002452 \[online 15 November 2010\]](#)

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

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Study finds mitochondrial dysfunction in autistic children

By Eddy Ball

A new exploratory study funded in part by NIEHS presents evidence that deficits in the ability to produce cellular energy are significantly more common in children with autism.

Published in JAMA, the findings from what may be the first study of its kind are the result of an interdisciplinary research effort by a team of scientists at the University of California, Davis (UCD). The team included NIEHS grantees [Irva Hertz-Picciotto, Ph.D.](#) (see [related story](#)), and [Isaac Pessah, Ph.D.](#), of the UCD Medical Investigation of Neurodevelopmental Disorders (MIND) Institute.



“If we find some kind of blood marker that is consistent with and unique to children with autism, maybe we can change the way we diagnose this difficult-to-assess condition,” Giulivi said as she looked forward to future research. (Photo courtesy of the University of California Regents)

Linked video:
[Watch interview with lead author Cecilia Giulivi \(4:42\)](#)
(Launches in new window)

Download Media Player: Flash [↗](#)

The [study](#) looked at biomarkers of mitochondrial function in blood samples from 20 children — ten diagnosed with autism and ten typically developing controls of similar age and demographic. The team randomly selected the autistic children from Northern California subjects who were previously enrolled in the NIEHS-funded 1,600-participant [Childhood Autism Risk from Genetics and the Environment \(CHARGE\) Study](#).

Although the differences between measures of mitochondrial function in subjects and controls were dramatic, the authors were understandably cautious about the interpretation of their findings. “More research is needed to understand the molecular causes of mitochondrial dysfunction and how this and other neurometabolic defects may contribute to autism or related phenotypes,” wrote lead author [Cecilia Giulivi, Ph.D.](#) Giulivi is a professor in the Department of Molecular Biosciences in the School of Veterinary Medicine at UCD and a recipient of an Autism Speaks Pilot Award that provided partial funding for the study.

A possible link between energy deficits and cognitive development

The researchers speculate that a lack of the ability to fuel the brain neurons, which consume high levels of energy second only to levels required by the heart, might trigger some of the cognitive deficits associated with autism. Mitochondria are the primary source of energy production in the cells, and mitochondrial dysfunction and resulting oxidative stress have been associated with a number of other neurological disorders.

The researchers found that mitochondria from children with autism consumed far less oxygen than mitochondria from the group of control children, a sign of lowered mitochondrial activity. Findings that hydrogen peroxide levels in autistic children were twice as high as in normal children support the concept that the cells of children with autism were exposed to higher oxidative stress.

According to Giulivi, mitochondrial diseases cause exercise intolerance, seizures, and cognitive decline, among other conditions. Some children will manifest disease symptoms and some will appear as sporadic cases. “Many of these characteristics are shared by children with autism,” she is quoted as saying in a Nov. 30 [press release](#) from UCD.

“Only one child with autism in this study fulfilled the diagnostic criteria for a definite mitochondrial respiratory chain disorder,” Giulivi said. “Collectively these results suggest that cumulative damage and oxidative stress over time may — through reduced capacity to generate functional mitochondria — influence the onset or severity of autism and its co-morbid symptoms.”

Looking to the future

Echoing the study’s call for further investigations, NIEHS Principal Investigator William Copeland, Ph.D., also expressed a need for more research. “This is a very preliminary study, and the high percentage of mitochondrial defects seen in this very small patient study is unprecedented and will need to be verified in a more expanded study,” observed Copeland, who is head of the NIEHS Mitochondrial DNA Repair Group in the Laboratory of Molecular Genetics.

Such future studies may benefit from new NIEHS-funded efforts to determine the best or most widely accepted cellular or biological measures that signal mitochondrial dysfunction more accurately in non-invasive or minimally invasive sample collections ([see related story](#)).

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“This important exploratory research addresses in a rigorous way an emerging hypothesis about potential mitochondrial dysfunction and autism,” said Cindy Lawler, Ph.D., NIEHS program administrator who oversees grants in the area of autism research. (Photo courtesy of Steve McCaw)

NIEHS to fund new mitochondrial dysfunction studies

By Eddy Ball

NIEHS issued a new [funding opportunity announcement \(FOA\)](#) Nov. 30 for projects to identify biomarkers for early detection of environmentally induced mitochondrial dysfunction. Applications will be accepted from Jan. 3 through Feb. 3.

Mitochondrial dysfunction results in deficits in cellular bioenergy production and is associated with numerous chronic diseases. It also may reflect, in part, the vulnerability of mitochondria to environmental influences.

NIEHS has committed \$2.5 million this year to fund between six and eight research projects to seek new markers of early mitochondrial dysfunction that results from environmental exposures or stressors.

According to the announcement, the new grant opportunity will stimulate the development of biomarkers of mitochondrial dysfunction in easily accessible tissues, including blood, buccal mucosa, and urine, by enhancing the basic understanding of how environmental stressors affect mitochondrial function. The new NIEHS grants will help investigators explore several important areas:

- Enhancing the understanding of how the more severe effects on mitochondrial function in target tissues relate to milder effects in surrogate tissues
- Understanding whether alterations in mitochondrial endpoints are adaptive or adverse — transient or persistent — effects
- Determining which endpoints signal early effects on mitochondrial function before more severe tissue phenotypes are apparent

NIEHS intends the funding to encourage development of biomarkers of mitochondrial dysfunction, using animal models and other experimental models that can help to identify environmental stressors that inhibit normal mitochondrial function. These models will then enable the development of approaches and candidate markers to serve as the basis for discovering biomarkers of early mitochondrial dysfunction in human population studies linking exposure to disease.

The new funding of mitochondrial biomarker research could help address some of the questions surrounding human diseases and help establish tools for further research to answer lingering questions about the role of the environment in mitochondrial dysfunction, both clinical and subclinical, in a range of conditions including autism ([see related story](#)).

Scientific Review Administrator [Leroy Worth, Ph.D.](#), is serving as peer review contact on the FOA, and Program Administrator [Dan Shaughnessy, Ph.D.](#), is providing scientific and research support.

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Casey presents at international meeting on alternatives for endocrine disruptors

By NICEATM

Warren Casey, Ph.D., deputy director of the [National Toxicology Program \(NTP\) Interagency Center for the Evaluation of Alternative Toxicological Methods \(NICEATM\)](#), traveled to Paris in late November to participate in an expert meeting to discuss *in vitro* methods for detecting substances that might interfere with normal hormone function.

Casey presented an update on NICEATM activities relevant to these types of test methods at the Eighth Meeting of the Validation Management Group for Non-animal Testing (VMG-NA). The Nov. 30 - Dec. 2 meeting was sponsored by the [Organisation of Economic Co-operation and Development \(OECD\)](#) and convened at the OECD headquarters in Paris.

Casey's presentation detailed the status of NICEATM-sponsored validation studies for two *in vitro* methods proposed for identifying endocrine disruptors that interfere with normal estrogen function. One method, the BG1 Luc ER TA (known also as the LUMI-CELL® ER assay) uses human ovarian cancer cells to identify substances that might increase or decrease estrogenic activity (i.e., estrogen agonists and antagonists).

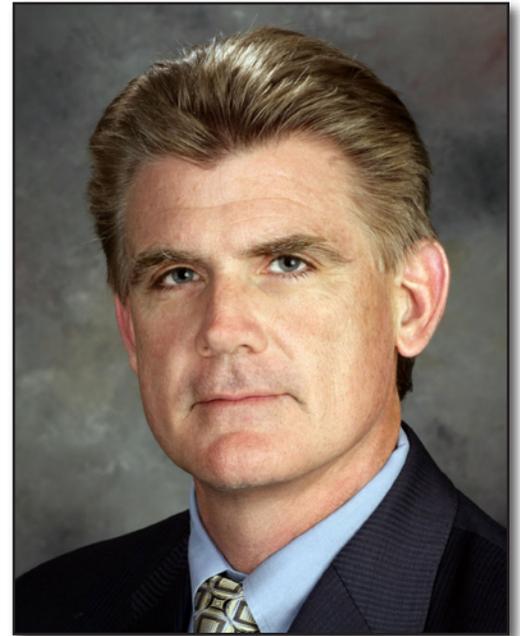
Likewise, the MCF-7 cell proliferation test method uses human breast cancer cells to accomplish the same goal. These efforts are a high priority for NICEATM and the NICEATM-supported Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM).

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

Concerns about endocrine disruptors

Endocrine disruptors are substances that interfere with the normal function of hormones in the endocrine system. Public health concerns have resulted largely from studies indicating that animal populations exposed to high levels of these substances have an increased incidence of reproductive and developmental abnormalities. While the impact of endocrine disruptors on human health remains poorly defined, these growing concerns warrant the availability of methods that can provide accurate and timely identification of potential endocrine disruptors.

The validation study for the MCF-7 assay, which involves participating laboratories from the U.S., Japan, and Korea, is ongoing. The validation study of the BG1 Luc ER TA, which included participating laboratories from the U.S., Europe, and Japan, was completed in 2010. Data from this study will be reviewed at an ICCVAM-sponsored independent peer review panel meeting taking place beginning in March.



*Warren Casey, Ph.D., deputy director of the NICEATM, participated in an expert discussion in Paris of *in vitro* methods of detecting endocrine disruptors. (Photo courtesy of Steve McCaw)*

NICEATM and ICCVAM will convene the panel meeting March 29-30. In addition to data from the validation studies, the panel will also consider ICCVAM draft test method recommendations on the usefulness and limitations of this test method for identifying potential estrogen agonists or antagonists.

Casey serves along with endocrine disruptor experts

In addition to presenting at the meeting, Casey served on the scientific committee for the meeting, along with experts in the field of endocrine disruption from the United States, Canada, Japan, Korea, and Europe.

Other ICCVAM-affiliated presenters at the meeting included Jack Fowle, Ph.D., of the Environmental Protection Agency (EPA), who is EPA's principal ICCVAM representative and a member of the ICCVAM Interagency Endocrine Disruptors Working Group. This group is currently working with NICEATM to prepare for the upcoming peer review panel meeting.

Documents will be provided to the panel and made available for public comment early next year. All publicly available documents and details about the meeting will be available on the NICEATM-ICCVAM website.

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New green safety testing methods available to identify ACD

By NICEATM

NIEHS has endorsed two new alternative safety-testing methods to determine if chemicals and products may cause allergic skin reactions, also known as allergic contact dermatitis (ACD). Skin diseases are the most common occupational disease category, and allergic reactions account for a large percentage of these cases.

The [Interagency Coordinating Committee on the Validation of Alternative Methods \(ICCVAM\)](#) recently evaluated and recommended the new methods, which are versions of the murine local lymph node assay (LLNA).

NIEHS/NTP Director Linda Birnbaum, Ph.D., endorsed the ICCVAM recommendations in a recent memorandum, in which she noted, "NIEHS and the [NTP](#) will promote and encourage use of the standard and nonradioactive versions of the LLNA for assessing the allergic contact dermatitis potential of chemicals and products."

The two new green technology methods provide both environmental and animal welfare advantages, compared to traditional test methods. Since these methods do not use radioactive reagents, they avoid the generation of radioactive waste and can be used by laboratories that are not licensed to use radioactive reagents. They also provide for improved animal welfare and use up to 50 percent fewer animals than traditional test methods.

ICCVAM and the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) conducted a comprehensive technical evaluation of the scientific validity of the two non-radioactive methods — the LLNA: 5-bromo-2-deoxyuridine-ELISA (LLNA:BrdU-ELISA), and the LLNA: Daicel Adenosine Triphosphate (LLNA:DA). ICCVAM concluded that the accuracy and reliability of the two methods support their use for safety and hazard assessments.

Protocols for the recommended LLNA methods and other ICCVAM-recommended test methods are available on the test method protocols page of the NICEATM-ICCVAM website (<http://iccvam.niehs.nih.gov/methods/protocols.htm>).

The U.S. Public Health Service Policy on Humane Care and Use of Laboratory Animals and Animal Welfare Act regulations require consideration of alternative methods that may reduce, refine, or replace animal use prior to the approval of procedures involving animals, and their use when determined scientifically appropriate. Since the new testing methods do not involve pain and distress compared to traditional testing methods, they will need to be considered and used for safety studies when determined appropriate.

Birnbaum has asked the NIEHS Institutional Animal Care and Use Committee, which oversees and evaluates all aspects of the NIEHS animal care and use program, to ensure that these alternative methods are always considered whenever applicable. Appropriate consideration and use of the methods will minimize animal use and provide for improved animal welfare while allowing investigators to conduct sound scientific research supporting the protection of human health.

Information on the NICEATM-ICCVAM evaluation of the nonradioactive LLNA methods is also available on the NICEATM-ICCVAM [website](#).

Background of the LLNA

The current recommendations are the latest from a series of evaluations of the LLNA by NICEATM and ICCVAM. In October 2009, ICCVAM forwarded recommendations to federal agencies for LLNA performance standards and an updated LLNA protocol that further reduces animal use by up to 50 percent. Based on a review of recent data, ICCVAM has also recommended that the LLNA can be used for testing nearly all chemicals and products, including pesticide formulations. NICEATM and ICCVAM proposed new and updated international test guidelines for the new LLNA versions that have now been adopted by the 33 member countries of the Organisation for Economic Co-operation and Development. NICEATM and ICCVAM are also currently evaluating several *in vitro* and *in chemico* methods for their potential to further reduce and eventually replace the need for animals for allergic contact dermatitis safety testing.

NICEATM provided scientific support and coordination for the ICCVAM Interagency Immunotoxicity Working Group (IWG) that evaluated the new LLNA versions and applications. The IWG is co-chaired by Abigail Jacobs, Ph.D., of the U.S. Food and Drug Administration (FDA) and Joanna Matheson, Ph.D., of the U.S. Consumer Product Safety Commission (CPSC). It includes scientists from the CPSC, the Environmental Protection Agency, FDA, NIEHS, and the National Institute for Occupational Safety and Health. NIEHS scientists Dori Germolec, Ph.D., William Stokes, D.V.M., and Warren Casey, Ph.D., DABT, contributed to the ICCVAM recommendations. Stokes is director of NICEATM and executive director of ICCVAM.

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Stokes presents at international meeting on alternatives for vaccine testing

By NICEATM

Rear Admiral William Stokes, D.V.M., the director of the National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), traveled to Langen, Germany, in December to share recommendations for reducing, refining, and eventually replacing animal use for the purpose of testing vaccines.

Stokes presented conclusions and recommendations from the NICEATM-sponsored “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,” which took place in September ([see story](#)).

He gave his presentation at a meeting titled, “Potency Testing of Veterinary Vaccines for Animals: The Way From *In Vivo* to *In Vitro*.” The Dec. 1-3 meeting was sponsored by the [Paul Ehrlich Institute](#), an agency of the German Federal Ministry of Health that promotes the quality, efficacy, and safety of biological medicinal products. The meeting was co-sponsored by the International Association for Biologicals and the [European Directorate for the Quality of Medicines and HealthCare](#).

Vaccines are vital and cost-effective public health tools used to prevent a wide range of serious and potentially fatal infectious diseases in people and animals. However, prior to the release of each production lot of an approved vaccine, testing is required to ensure that the particular lot is safe and effective. Such testing requires the use of large numbers of animals, and can result in some animals experiencing significant pain and distress.



Pictured above, left to right, are meeting participants Robin Levis, Ph.D., of the Food and Drug Administration’s (FDA) Center for Biologics Evaluation and Research; NICEATM Director William Stokes, D.V.M.; Donna Gatewood, D.V.M., of the USDA Center for Veterinary Biologics; Juan Arciniega, D.Sc., of the U.S. Food and Drug Administration’s Center for Biologics Evaluation and Research; Jean-Marc Spieser of the European Directorate for the Quality of Medicines and HealthCare; acting ICCVAM Chair Jodie Kulpa-Eddy, D.V.M.; and Carmen Jungback, D.V.M., of the Paul Ehrlich Institute. (Photo courtesy of William Stokes)

Efforts to reduce animal testing

In recent years, efforts have increased to develop and validate alternative methods that reduce, refine (decrease pain and distress), and replace the use of animals for vaccine potency and safety testing. These efforts are a high priority for NICEATM and the NICEATM-supported Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM).

Stokes’ presentation pointed to priorities for future research and development efforts needed to advance alternatives for vaccine potency and safety testing, including:

- Replacement alternatives such as *in vitro* protective antigen quantification assays
- Refinement alternatives, including vaccination followed by *in vitro* antibody quantification, and developing earlier more humane endpoints for both safety and potency testing
- Reduction alternatives, such as identifying and reducing sources of variation to allow for the use of fewer animals while still maintaining statistical power of the assay

Recommendations from the NICEATM-sponsored workshop also addressed how to expedite global progress in developing alternatives for human and veterinary vaccine testing, including improved dissemination and accessibility of information on new initiatives, documents, and guidances; international harmonization of principles for validation of alternative vaccine test methods; harmonizing testing procedures for individual protective antigens; encouraging product-specific validation of available alternative methods by vaccine manufacturers; and expanding support for research and development into new alternative methods.

NICEATM and ICCVAM have a commitment to building global partnerships to advance new alternative testing methods, and participation in events such as the recent Langen meeting are an important part of developing those partnerships.

Highlights of the Langen meeting

In addition to presenting at the meeting, Stokes, who is a U.S. Public Health Service Commissioned Corps officer and an Assistant Surgeon General, served on the scientific committee for the meeting, along with experts in the fields of alternative methods development and vaccine testing from the United States and Europe.

Other presenters at the Langen meeting affiliated with ICCVAM or ICCVAM member agencies included: Jodie Kulpa-Eddy, D.V.M., of the U.S. Department of Agriculture (USDA), who is acting chair of ICCVAM; Juan Arciniega, D.Sc., of the U.S. Food and Drug Administration's Center for Biologics Evaluation and Research, a member of the ICCVAM Interagency Biologics Working Group; Donna Gatewood, D.V.M., of the USDA; and Karen Brown, Ph.D., of Pair O'Docs Enterprises, who is member of ICCVAM's scientific advisory committee and served as chair of a 2007 ICCVAM-sponsored independent peer review panel.

Proceedings of the Langen meeting will be published by the Paul Ehrlich Institute in 2011. Proceedings of the NICEATM-sponsored workshop will be also published in 2011 as a dedicated issue of *Procedia in Vaccinology*.

The ICCVAM Interagency Biologics Working Group is currently addressing implementation of the recommendations from the ICCVAM workshop. Presentation slides and more information about the ICCVAM workshop are available on the NICEATM-ICCVAM website at <http://iccvam.niehs.nih.gov/meetings/BiologicsWksp-2010/BiologicsWksp.htm>.

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This month in EHP

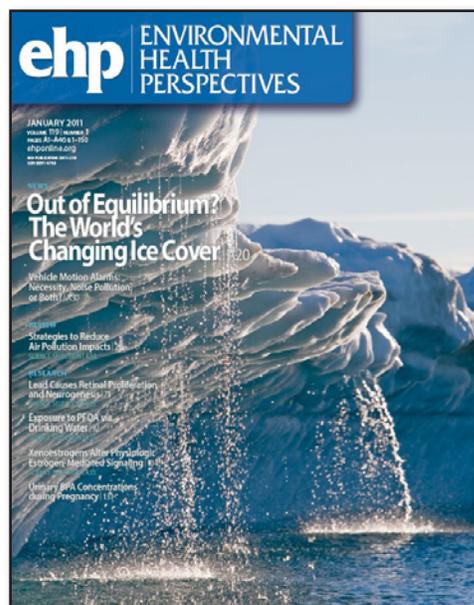
By Melissa Kerr

With a vivid cover photo of a melting iceberg, the January issue of [Environmental Health Perspectives \(EHP\)](#) revisits climate change. The news article "Out of Equilibrium? The World's Changing Ice Cover" discusses our current understanding of how and why the earth's cryosphere is changing as well as the impact of those changes on human health. The second story, "Vehicle Motion Alarms: Necessity, Noise Pollution, or Both?" weighs the safety benefits and noise pollution drawbacks of warning signals including backup beepers and artificial engine noise for quiet-running electric vehicles.

In this month's [podcast](#), host Ashley Ahearn speaks with [Åke Bergman](#), head of the Department of Materials and Environmental Chemistry at Stockholm University. They discuss the San Antonio Statement on Brominated and Chlorinated Flame Retardants, which was published in the December issue of EHP.



<http://twitter.com/ehponline>



Among the reviews and research studies included in this issue are:

- Strategies to Reduce Air Pollution Impacts
- Lead Causes Retinal Proliferation and Neurogenesis
- Exposure to PFOA via Drinking Water
- Xenoestrogens Alter Physiologic Estrogen-mediated Signaling
- Urinary BPA Concentrations During Pregnancy

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

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Susan Amara to present distinguished lecture

By Eddy Ball

The NIEHS 2010-2011 Distinguished Lecture Series returns to the fascinating world of neuroscience with its next talk Jan. 11 by neurobiologist Susan Amara, Ph.D., on “The Ins and Outs of Neurotransmitter Transporters.”

[Amara](#) is Thomas Detre Professor and chair of the Department of Neurobiology at the University of Pittsburgh, as well as co-director of the Center for Neuroscience there. She is currently the president of the Society for Neuroscience.

A Howard Hughes Medical Institute alumni investigator, Amara has received many honors for her work, including the John Jacob Abel Award from the American Society of Pharmacology and Experimental Therapeutics and a McKnight Neuroscience Investigator Award. She received a 1997 MERIT Award from the National Institute on Drug Abuse, and she was elected to the National Academy of Sciences in 2004.

Amara lists her major research interests as the structure, regulation, and cellular physiology of two families of sodium-dependent neurotransmitter transporters — the biogenic amine and the excitatory amino acid carriers. The dopamine, norepinephrine, and serotonin transporters are well-established targets for addictive drugs including cocaine and amphetamines, as well as for therapeutic antidepressants.

Her lab uses molecular genetic, electrophysiological, and cell biological approaches to explore the relationships between neurotransmitter transporter structure, substrate transport, inhibitor binding, and ion permeation.

NIEHS Ion Channel Physiology Group Principal Investigator [Jerrel Yakel, Ph.D.](#), will host the talk, which begins at 11:00 a.m. in Rodbell Auditorium.

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*Upcoming Distinguished Lecturer Susan Amara
(Photo courtesy of Susan Amara)*

Extramural papers of the month

By Jerry Phelps

- [BPA exposure and oocyte quality](#)
- [Freeway proximity and autism](#)
- [A simple sensor for explosive chemicals](#)
- [Blood DNA methylation related to heart disease and stroke](#)



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

BPA exposure and oocyte quality

A small study conducted by NIEHS-supported researchers at the University of California, San Francisco has determined that as blood bisphenol A (BPA) levels rise, the quality of oocytes from women undergoing *in vitro* fertilization declines. As blood levels of BPA doubled, the percentage of eggs that fertilized normally declined by 50 percent.

BPA levels and fertilization rates were analyzed for 26 women undergoing *in vitro* fertilization during 2007 and 2008. The women were a subgroup of a larger study evaluating the effects of trace exposures to toxic metals on reproductive health.

Though the size of the study is small, the results indicate a negative effect of BPA on reproduction and fertility that may carry over to the general population. Further research on a much larger cohort of participants is necessary to confirm these findings in the general population, but given the widespread nature of BPA exposure in the U.S., even a modest effect on reproduction demonstrates a substantial concern according to the researchers.

Citation: [Fujimoto VY, Kim D, Vom Saal FS, Lamb JD, Taylor JA, Bloom MS](#). 2010. Serum unconjugated bisphenol A concentrations in women may adversely influence oocyte quality during *in vitro* fertilization. *Fertil Steril*; doi:10.1016/j.fertnstert.2010.11.008 [online 4 December 2010]

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Freeway proximity and autism

New research findings from a study sponsored by NIEHS suggest that babies born to mothers who live close to freeways have double the risk of developing autism compared to other children. The study examined almost 600 children ages 2-5 from Los Angeles, San Francisco, and Sacramento, Calif. About half the children had autism. Those whose homes were less than 1,000 feet from a freeway were about twice as likely to have autism.

Little is known about environmental contributions to autism, but oxidative stress and inflammation have been linked to the disorder. Previous basic research has demonstrated that traffic-related air pollution causes oxidative damage and increases inflammatory signaling pathways.

In the current study, 304 children who had autism were compared to 259 typically developing children. The study participants were enrolled in the Childhood Autism Risks from Genetics and the Environment

(CHARGE) study. After adjusting for socioeconomic and demographic factors, the mother's address, taken from the birth record, was more likely to be near a freeway (less than 309 meters) for cases as compared to controls. Autism was also associated with residential proximity to a freeway during the third trimester; however, living near other major roads was not associated with autism.

Citation: Volk HE, Hertz-Picciotto I, Delwiche L, Lurmann F, McConnell R. 2010. Residential Proximity to Freeways and Autism in the CHARGE study. *Environ Health Perspect*; doi:10.1289/ehp.1002835 [Online 13 December 2010]

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A simple sensor for explosive chemicals

University of Illinois chemists have developed a simple device to detect an explosive like those used in several recent unsuccessful attempts to bring down airliners. The device could lead to an inexpensive and easy-to-use detector for luggage and passenger screening in airports.

The explosive, triacetone triperoxide (TATP), is easily prepared from products readily available, but it is very difficult to detect with standard detection methods. The researchers developed a colorimetric sensor assay that can detect very low levels of TATP vapor, as low as 2 parts per billion, in a matter of seconds. The sensor array consists of 16 colored dots on an inert plastic film. An acid catalyst breaks down TATP into detectable components that cause the pigments to change color.

The array is uniquely sensitive to TATP and is unaffected by temperature, humidity, or exposure to other chemicals, such as those found in detergents or personal care products. The chemists made a hand-held prototype that is just as effective as their laboratory model. The hand-held sensor is now being commercialized by iSense, a sensor manufacturer based in Palo Alto, Calif.

Citation: Lin H, Suslick KS. 2010. A colorimetric sensor array for detection of triacetone triperoxide vapor. *J Am Chem Soc* 132(44):15519-15521.

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Blood DNA methylation related to heart disease and stroke

NIEHS-supported epidemiologists at Harvard University found that blood DNA methylation is linked to the risk of ischemic heart disease and stroke in a population of 712 elderly subjects in the Boston-area Normative Aging Study.

The team measured blood cell DNA methylation of Long Interspersed Nucleotide Element-1 (LINE-1) repetitive elements by polymerase chain reaction pyrosequencing. They estimated relative risks for ischemic heart disease and stroke at baseline and again five years later, and also for mortality from ischemic heart disease.

LINE-1 hypomethylation was associated with baseline heart disease and stroke (relative risk = 2.1 and 2.5 respectively). In participants free of disease, hypomethylation was associated with higher risk for developing ischemic heart disease (relative risk = 4.1) or stroke (relative risk = 5.7). In the entire cohort, subjects with hypomethylation were about three times more likely to die of ischemic heart disease or stroke.

The researchers conclude that as standardized assays become more readily available, DNA methylation analysis may contribute to better cardiovascular risk estimation. These results add to the importance of ongoing endeavors in developing interventions and treatments that act through epigenetic mechanisms.

Citation: [Baccarelli A, Wright R, Bollati V, Litonjua A, Zanobetti A, Tarantini L, Sparrow D, Vokonas P, Schwartz J.](#) 2010. Ischemic heart disease and stroke in relation to blood DNA methylation. *Epidemiology* 21(6):819-828.

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

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Intramural papers of the month

By Ritu Rana and Robin Arnette

- [Paused Pol II regulates gene activity](#)
- [Estrogen receptor alpha has cell specific roles in the endometrium](#)
- [Involvement of human CYP epoxygenases in hypertension and kidney damage](#)
- [DNA polymerase delta replicates on lagging strand](#)

Paused Pol II regulates gene activity

Recent research indicates that a main function of paused RNA polymerase II (Pol II) is to compete with nucleosomes for occupancy of a gene promoter. This action prevents the formation of chromatin, which represses gene activation. The new mechanism offers an explanation as to why some genes remain constitutively active, while others are highly regulated and activated only in response to external stimuli.

The work, completed by investigators from NIEHS and the Lieber Institute for Brain Development at Johns Hopkins University, also found that the DNA sequence surrounding the promoter influences the gene's function and how it will be regulated. Housekeeping genes that should be continuously active, contain a chromatin-unfriendly sequence and, as a result, exhibit low nucleosomal occupancy on their gene start sites. In contrast, highly regulated genes exhibit a chromatin-friendly sequence that invites nucleosomes or chromatin to bind to the promoter and prevent transcription.

Using genome wide analysis of Pol II recruitment and nucleosomal occupancy in *Drosophila* cells, the study proposes that at tightly regulated genes, paused Pol II out-competes nucleosomes for promoter occupancy and thus allows efficient gene activation in response to environmental cues.

Citation: [Gilchrist DA, Dos Santos G, Fargo DC, Xie B, Gao Y, Li L, Adelman K.](#) 2010. Pausing of RNA polymerase II disrupts DNA-specified nucleosome organization to enable precise gene regulation. *Cell* 143(4):540-551.

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Estrogen receptor alpha has cell specific roles in the endometrium

Previous findings had shown estrogen receptor alpha (ERalpha) was required for endometrial hyperplasia and had assumed epithelial proliferative mechanisms utilized epithelial ER. Researchers from NIEHS, the Sloan-Kettering Institute, and the University of Texas M.D. Anderson Cancer Center have now determined that the role of ERalpha differs in specific cells. ERalpha can prevent uterine epithelial cell apoptosis, but is not needed for cell proliferation.

The investigators generated a uterine epithelial-specific ER- α knockout (UtEpialphaERKO) mouse line to evaluate the role of epithelial ERalpha in tissue proliferation. 17 β -estradiol (E2) is an ovarian hormone that prepares the uterus for the developing pregnancy by inducing hyperplasia in uterine endometrium. Previous studies have shown that E2 stimulates uterine proliferation in an ERalpha-dependent manner.

Researchers found that in the absence of epithelial ERalpha, uterine proliferation still occurs when stromal ERalpha responds to the E2 signal by production of certain growth factor(s) such as Insulin like growth factor (IGF-1) that then mediate the epithelial proliferation. Conversely, the apoptosis inhibitor Birc1a was not induced in the absence of epithelial ERalpha, leading to apoptosis.

Further studies are required to determine any clinical implications of this differential role of ERalpha in diseases such as endometriosis, endometrial hyperplasia, and cancer, in addition to responses to selective estrogen receptor modulators (SERM).

Citation: [Winuthayanon W, Hewitt SC, Orvis GD, Behringer RR, Korach KS. 2010. Uterine epithelial estrogen receptor alpha is dispensable for proliferation but essential for complete biological and biochemical responses. Proc Natl Acad Sci USA 107\(45\):19272-19277.](#)

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Involvement of human CYP epoxygenases in hypertension and kidney damage

A report in The FASEB Journal proposes that human endothelial cytochrome P450 (CYP), when overexpressed in transgenic (Tr) mice, reduces vascular tone and improves kidney injury associated with high blood pressure (hypertension). CYP exerts this control via synthesis of epoxyeicosatrienoic acids (EETs), which are known vasodilators and also have organ protective effects. The results represent a potentially new method for controlling hypertension and reducing renal injury in mice, and could potentially lead to new treatments for humans with these common disorders.

In a collaborative effort by investigators from several research institutions, including NIEHS, team members overexpressed CYP2J2 and CYP2C8 epoxygenases in endothelial cells of C57Bl/6 mice to increase EET biosynthesis. In *in vitro* studies, the researchers isolated rodent blood vessels and subjected them to treatments with angiotensin II, a known vasoconstrictor. The vasoconstrictor elicited a weaker constriction in renal arterioles in transgenic mice than in wild type controls. The vasodilator acetylcholine yielded enhanced dilation in transgenic mice compared to wild type controls.

In *in vivo* studies, the team fed wild type and transgenic mice a high-salt diet and subjected them to treatment with angiotensin II to induce hypertension. The transgenic mice exhibited lower blood pressure and had less kidney damage than wild type mice. Together, these experiments suggest that CYP products play an important role in the regulation of blood pressure and renal injury.

Citation: Lee CR, Imig JD, Edin ML, Foley J, DeGraff LM, Bradbury JA, Graves JP, Lih FB, Clark J, Myers P, Perrow AL, Lepp AN, Kannon MA, Ronnekleiv OK, Alkayed NJ, Falck JR, Tomer KB, Zeldin DC. 2010. Endothelial expression of human cytochrome P450 epoxygenases lowers blood pressure and attenuates hypertension-induced renal injury in mice. *FASEB J* 24(10):3770-3781.

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DNA polymerase delta replicates on lagging strand

Studies using budding yeast mutants have determined that DNA polymerase delta (Pol delta) primarily replicates DNA on the lagging strand throughout the entire genome. The work, performed by scientists from NIEHS and the University of North Carolina, Chapel Hill, offers evidence regarding the mechanism of DNA replication.

The research team generated a Pol delta mutant (*pol3-L612M*) which creates a diagnostic mutation pattern depending on the the strand that this Pol copy in double-strand DNA, and then used a technique called deep sequencing to establish a pattern of base substitution mutations produced by the mutant. Sequencing of 16 genomes produced 1,206 base pair substitutions that were identified as “hotspots” for Pol delta replication errors.

This many mutations mapped throughout the genome enabled researchers to track which DNA strand was synthesized by the error-prone Pol delta. Near each origin, where the identification of leading and lagging can be unequivocally made based on direction towards the closest origin, direction-specific mutation signature clearly indicated Pol delta being exclusive lagging strand polymerase. However, closer to the midway between the neighboring origins, where the two replication forks meet and lagging strand synthesis could go in either direction, the direction-specific signature faded.

Altogether, the data suggested that Pol delta was responsible for the bulk of lagging strand synthesis throughout the genome, while Pol epsilon, by default is responsible for leading strand synthesis.

Citation: Larrea AA, Lujan SA, Nick McElhinny SA, Mieczkowski PA, Resnick MA, Gordenin DA, Kunkel TA. 2010. Genome-wide model for the normal eukaryotic DNA replication fork. *Proc Natl Acad Sci USA* 107(41):17674-17679.

(Ritu Rana, Ph.D., is a visiting fellow in the NIEHS Laboratory of Toxicology and Pharmacology Human Metabolism Group.)

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2010 papers of the year

By Matt Goad

Of the more than 2,900 papers published by NIEHS-supported researchers in 2010, 21 publications were chosen as papers of the year:

- Prenatal exposure to phthalates is associated with reduced masculine behavior in boys
- Obesity is a tumor promoter
- Fetal and early life exposures to BPA may increase the risk of cancer
- Mother's exposure to urban air pollutants affects children's cognitive abilities
- Researchers map the first human epigenome
- Living, breathing lung-on-a-chip
- Flame retardants linked to reduced human fertility
- Arsenic-related mortality in Bangladesh
- Genetic studies identify DNA sequences associated with lung function
- Acetaminophen-induced transcriptional changes predict liver injury
- Early-life exposures are linked to development of uterine fibroids
- Stem cell survival advantage toward arsenic drives malignant transformation
- Cholesterol trafficking linked to inflammatory response
- Genome instability due to ribonucleotide incorporation into DNA
- Gender differences in glucocorticoid-mediated inflammation
- Paused Pol II regulates gene activity
- Effects of low dose atrazine on pubertal timing and prostate development of male rats
- Genetic and epigenetic mechanisms in liver tumors of oxazepam-exposed mice
- Useful immunohistochemical markers of tumor differentiation
- Arsenic, stem cells and the developmental basis of adult cancer
- Cancer in experimental animals exposed to arsenic and arsenic compounds

Prenatal exposure to phthalates is associated with reduced masculine behavior in boys

University of Rochester researchers and NIEHS grantees Shanna Swan, Ph.D., and Bernard Weiss, Ph.D., reported for the first time that prenatal exposure to phthalates causes reduced masculine behavior in boys.

Mothers, whose urine had been analyzed for phthalates in mid-pregnancy, completed a questionnaire, including the Pre-School Activities Inventory used to assess gender differences in play behavior. The results showed that concentrations of dibutyl phthalate and diethylhexyl phthalate metabolites in the mothers' urine samples were statistically associated with decreased masculine play behavior in boys who were an average of five years old at the time of the assessment.

Citation: Swan SH, Liu F, Hines M, Kruse RL, Wang C, Redmon JB, Sparks A, Weiss B. 2010. Prenatal phthalate exposure and reduced masculine play in boys. *Int J Androl* 33(2):259-269.

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Obesity is a tumor promoter

Scientists at the University of California, San Diego reported the confirmation that obesity acts as a tumor promoter, in a January 2010 publication in the prestigious journal *Cell*. The findings suggest that anti-inflammatory drugs taken routinely by millions of people may also reduce the risk of cancer in those at high risk due to obesity and other factors. The research was jointly supported by an NIEHS grant and the Superfund Research Program.

The research team led by Michael Karin, Ph.D., found that liver cancer is promoted by a chronic inflammatory state that coincides with obesity. Liver cancer development was dependent on two well-known inflammatory factors, IL-6 and tumor necrosis factor. These inflammatory cytokines caused liver inflammation and activation of an oncogenic transcription factor known as STAT3.

Citation: Park EJ, Lee JH, Yu GY, He G, Ali SR, Holzer RG, Osterreicher CH, Takahashi H, Karin M. 2010. Dietary and genetic obesity promote liver inflammation and tumorigenesis by enhancing IL-6 and TNF expression. *Cell* 140(2):197-208.

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Fetal and early life exposures to BPA may increase the risk of cancer

NIEHS-funded researchers, using an American Recovery and Reinvestment Act (ARRA) supplement, demonstrated that regardless of route of exposure to bisphenol A (BPA), the effect on rats' prostates is the same. This has been a critical point of contention.

Serum BPA was delivered by injection and by oral exposure to neonatal rats. No matter the method of exposure, prostates from the aged rats exhibited nearly identical, heightened susceptibility to prostate intraepithelial neoplasia, thought to be a precursor to cancer.

Citation: Prins GS, Ye SH, Birch L, Ho SM, Kannan K. 2010. Serum bisphenol A pharmacokinetics and prostate neoplastic responses following oral and subcutaneous exposures in neonatal Sprague-Dawley rats. *Reprod Toxicol*; doi:10.1016/j.reprotox.2010.09.009 [Online 8 October 2010].

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Mother's exposure to urban air pollutants affects children's cognitive abilities

An NIEHS-supported study carried out in Krakow, Poland, reported prenatal exposure to air pollutants adversely affected the cognitive development of children at age 5. These findings confirmed a similar study conducted earlier in New York City.

The study was conducted in a cohort of 214 children born to healthy non-smoking women in Krakow, Poland, between 2001 and 2006. During pregnancy, the mothers wore small backpack-mounted personal air monitors to estimate their babies' exposures to polycyclic aromatic hydrocarbons (PAHs). PAHs are released into the air when fossil fuels are burned for purposes such as transportation, heating, and energy production.

At age 5, the children took a standard intelligence examination. Children in the high exposure group scored lower on the intelligence exam by about four IQ points.

Citation: Edwards SC, Jedrychowski W, Butscher M, Camann D, Kieltyka A, Mroz E, Flak E, Li Z, Wang S, Rauh V, Perera F. 2010. Prenatal exposure to airborne polycyclic aromatic hydrocarbons and children's intelligence at 5 years of age in a prospective cohort study in Poland. *Environ Health Perspect* 118(9):1326-1331.

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Researchers map the first human epigenome

A comparison of the epigenomes of embryonic stem cells and fibroblasts shows a pattern of methylation unique to stem cells, according to a study supported by NIEHS. The novel methylation pattern may help to explain how stem cells maintain their pluripotent state.

The research team developed a high-throughput method to determine the methylation status of every cytosine molecule in the genome and to layer the resulting epigenomic map onto the genome it regulates. The technique was then applied to human fibroblasts and embryonic stem cells to determine if the epigenomes differed between differentiated cells that perform a specific job and cells that have the potential to become any cell type.

This study provides the first complete high-resolution map of an epigenome superimposed on the human genome. This knowledge could be extremely valuable for understanding and developing treatments for diseases.

Citation: Lister R, Pelizzola M, Dowen RH, Hawkins RD, Hon G, Tonti-Filippini J, Nery JR, Lee L, Ye Z, Ngo QM, Edsall L, Antosiewicz-Bourget J, Stewart R, Ruotti V, Millar AH, Thomson JA, Ren B, Ecker JR. 2009. Human DNA methylomes at base resolution show widespread epigenomic differences. *Nature* 462(7271):315-322.

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Living, breathing lung-on-a-chip

NIEHS-supported researchers at the Wyss Institute for Biologically Inspired Engineering at Harvard University developed a device that mimics a living and breathing human lung on a microchip roughly the size of a quarter.

The lung-on-a-chip device uses a new approach to tissue engineering that places tissue, from the lining of the alveoli and blood vessels that surround them, across a porous membrane. Air flows across the lung cells while culture medium, mimicking blood, is pumped through the capillaries. Mechanical stretching of the device mimics the expansion and contraction of the lungs during breathing.

The device has the potential to be a valuable research tool for testing the effects of environmental agents, and the absorption, safety, and efficacy of drug candidates.

Citation: Huh D, Matthews BD, Mammoto A, Montoya-Zavala M, Hsin HY, Ingber DE. 2010. Reconstituting organ-level lung functions on a chip. *Science* 328(5986):1662-1668.

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Flame retardants linked to reduced human fertility

Women exposed to high levels of flame retardants take longer to become pregnant, according to an NIEHS-funded study at the University of California, Berkeley. This is the first study to show decreases in human fertility related to the chemicals.

Polybrominated diphenyl ethers, or PBDEs, are a class of flame retardants found in many consumer products, such as foam cushions in furniture, carpet padding, clothing, and electronics. The compounds accumulate in fatty tissue and laboratory animal studies have identified them as endocrine disruptors.

More than 97 percent of the women participating in the study had measureable levels of PBDEs in their blood. With each tenfold increase in the blood level, the odds of becoming pregnant reduced by 30 percent.

Citation: Harley KG, Marks AR, Chevrier J, Bradman A, Sjodin A, Eskenazi B. 2010. PBDE concentrations in women's serum and fecundability. *Environ Health Perspect* 118(5):699-704.

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Arsenic-related mortality in Bangladesh

NIEHS-supported researchers reported that 21.4 percent of all deaths in the Araihaazar region of Bangladesh can be attributed to well water arsenic concentrations greater than 10 micrograms per liter. Their findings are from the first prospective study to investigate the link between arsenic exposure and mortality, and are published online in *The Lancet*.

A unique feature of this study is that it includes participants at both the low and high ends of the dose-response curve. For people exposed to the highest doses of arsenic, all-cause mortality was nearly 70 percent higher, relative to those exposed to less than the World Health Organization standard of 10 micrograms per liter.

Citation: Argos M, Kalra T, Rathouz PJ, Chen Y, Pierce B, Parvez F, Islam T, Ahmed A, Rakibuz-Zaman M, Hasan R, Sarwar G, Slavkovich V, van Geen A, Graziano J, Ahsan H. 2010. Arsenic exposure from drinking water, and all-cause and chronic-disease mortalities in Bangladesh (HEALS): a prospective cohort study. *Lancet* 376(9737):252-258.

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Genetic studies identify DNA sequences associated with lung function

A collaborative research effort, led by NIEHS scientists, identified genetic factors that increase the risk of impaired lung function. The study provides insight into the biological mechanisms that contribute to pulmonary function and possibly to the pathogenesis of chronic lung diseases, such as asthma and chronic obstructive pulmonary disease (COPD).

Stephanie London, M.D., and colleagues conducted analyses of data generated from several studies that involved more than 20,000 participants. Using this data, the authors identified genetic variations in eight previously unrecognized DNA regions that alter lung function.

The investigators determined that individuals carrying the identified genetic variations have lower pulmonary function and are at greater risk for developing COPD. Moreover, predictions involving these genetic alterations were consistent with those for known risk factors associated with decreased lung function, such as smoking and increasing age.

Citation: Hancock DB, Eijgelsheim M, Wilk JB, Gharib SA, Loehr LR, Marcianti KD, Franceschini N, van Durme YM, Chen TH, Barr RG, Schabath MB, Couper DJ, Brusselle GG, Psaty BM, van Duijn CM, Rotter JI, Uitterlinden AG, Hofman A, Punjabi NM, Rivadeneira F, Morrison AC, Enright PL, North KE, Heckbert SR, Lumley T, Stricker BH, O'Connor GT, London SJ. 2010. Meta-analyses of genome-wide association studies identify multiple loci associated with pulmonary function. *Nat Genet* 42(1):45-52.

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Acetaminophen-induced transcriptional changes predict liver injury

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

The authors examined changes in human peripheral blood (PB) gene expression in response to a dose of acetaminophen that did not induce detectable levels of liver injury. They observed a distinct transcriptional signature, including downregulation of genes associated with oxidative phosphorylation, and metabolic changes that led to increased serum lactate levels.

The identification of acetaminophen-induced transcriptional and metabolic signatures in human PB may address the need for better biomarkers of DILI. These expression profiles may assist clinicians and provide more meaningful liver safety data in clinical trials of new drugs.

Citation: Fannin RD, Russo M, O'Connell TM, Gerrish K, Winnike JH, Macdonald J, Newton J, Malik S, Sieber SO, Parker J, Shah R, Zhou T, Watkins PB, Paules RS. 2010. Acetaminophen dosing of humans results in blood transcriptome and metabolome changes consistent with impaired oxidative phosphorylation. *Hepatology* 51(1):227-236.

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Early-life exposures are linked to development of uterine fibroids

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

Fibroids, the most common indication for hysterectomies in the United States, are benign smooth-muscle tumors, associated with pelvic pain, heavy bleeding, and reproductive problems. This study associated increased risk of fibroids diagnosed by age 35 with several factors, including being fed soy formula during infancy.

Citation: D'Aloisio AA, Baird DD, DeRoo LA, Sandler DP. 2010. Association of intrauterine and early-life exposures with diagnosis of uterine leiomyomata by 35 years of age in the sister study. *Environ Health Perspect* 118(3):375-381.

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Stem cell survival advantage toward arsenic drives malignant transformation

Researchers from the National Cancer Institute at NIEHS, now with National Toxicology Program, reported that the carcinogen arsenic targets stem cells for transformation, eventually producing cancers enriched in cancer stem cells. This is facilitated by a stem cell survival advantage toward arsenic during malignant transformation.

These observations further strengthen the argument that arsenic most likely targets cells that have either a stem or progenitor phenotype and undergo survival selection during arsenic-induced malignant transformation.

Citation: Tokar EJ, Qu W, Liu J, Liu W, Webber MM, Phang JM, Waalkes MP. 2010. Arsenic-specific stem cell selection during malignant transformation. *J Natl Cancer Inst.* 102(9):638-649.

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Cholesterol trafficking linked to inflammatory response

Investigators from the NIEHS Laboratory of Respiratory Biology report that Myeloid differentiation primary response protein 88 (MyD88), an adaptor protein in innate immunity signaling pathways, is required for cholesterol export from cells and couples cholesterol export to inflammation. They found that apolipoprotein A-I (apoA-I), the major protein component of high-density lipoprotein (HDL) particles, elicits MyD88-dependent inflammatory signals in macrophages.

This work supports a new paradigm in which the innate immune response acts as a physiologic signal in cholesterol homeostasis. Whereas inflammation is generally thought to promote atherosclerosis, the authors provide evidence that immune pathways may also be required for removal of cholesterol from vessel walls.

Citation: Smoak KA, Aloor JJ, Madenspacher J, Merrick BA, Collins JB, Zhu X, Cavigliolo G, Oda MN, Parks JS, Fessler MB. 2010. Myeloid differentiation primary response protein 88 couples reverse cholesterol transport to inflammation. *Cell Metab* 11(6):493-502.

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Genome instability due to ribonucleotide incorporation into DNA

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

When researchers at the NIEHS and Umea University in Sweden recently tested these ideas, the results established three important facts about DNA replication: Ribonucleotides are indeed incorporated during replication *in vivo*; the ribonucleotides are normally removed by RNase H2-dependent repair; and defective repair causes cellular stress and genome instability.

Citation: Nick McElhinny SA, Kumar D, Clark AB, Watt DL, Watts BE, Lundstrom EB, Johansson E, Chabes A, Kunkel TA. 2010. Genome instability due to ribonucleotide incorporation into DNA. *Nat Chem Biol* 6(10):774-781.

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Gender differences in glucocorticoid-mediated inflammation

Research performed by scientists from NIEHS and Wake Forest University School of Medicine suggests that glucocorticoids, stress-induced steroids that regulate intermediary metabolism, may contribute to the development, progression, or susceptibility to inflammatory diseases in a gender-specific manner. This finding offers a possible explanation for why more females tend to have certain inflammatory diseases.

This work determined glucocorticoids regulate more liver genes in inflammatory pathways in males than females, suggesting that the failure by females to mount an adequate glucocorticoid inflammatory response may lead to more autoimmune diseases in women.

Citation: Duma D, Collins JB, Chou JW, Cidlowski JA. 2010. Sexually dimorphic actions of glucocorticoids provide a link to inflammatory diseases with gender differences in prevalence. *Sci Signal* 3(143):ra74.

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Paused Pol II regulates gene activity

Recent research, completed by investigators from NIEHS and the Lieber Institute for Brain Development at Johns Hopkins University, indicates that a main function of paused RNA polymerase II (Pol II) is to compete with nucleosomes for occupancy of a gene promoter. This action prevents the formation of chromatin, which represses gene activation. The new mechanism offers an explanation as to why some genes remain constitutively active, while others are highly regulated and activated only in response to external stimuli.

Housekeeping genes that should be continuously active contain a chromatin-unfriendly sequence and, as a result, exhibit low nucleosomal occupancy on their gene start sites. In contrast, highly regulated genes exhibit a chromatin-friendly sequence that invites nucleosomes or chromatin to bind to the promoter and prevent transcription.

Using genome-wide analysis of Pol II recruitment and nucleosomal occupancy in *Drosophila* cells, the study proposes that at tightly regulated genes, paused Pol II outcompetes nucleosomes for promoter occupancy and thus allows efficient gene activation in response to environmental cues.

Citation: Gilchrist DA, Dos Santos G, Fargo DC, Xie B, Gao Y, Li L, Adelman K. 2010. Pausing of RNA polymerase II disrupts DNA-specified nucleosome organization to enable precise gene regulation. *Cell* 143(4):540-551.

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Effects of low dose atrazine on pubertal timing and prostate development of male rats

In a study partly funded by NIEHS, researchers concluded that prenatal exposure to metabolites of the herbicide atrazine can cause chronic prostatitis in Long-Evans rats.

Pregnant rats were treated with an atrazine metabolite mixture consisting of atrazine and its environmental metabolites diaminochlorotriazine, hydroxyatrazine, deethylatrazine, and deisopropylatrazine. Exposed males demonstrated a significant delay in preputial separation and a significant increase in incidence and severity of inflammation in the prostate.

Citation: Stanko JP, Enoch RR, Rayner JL, Davis CC, Wolf DC, Malarkey DE, Fenton SE. 2010. Effects of prenatal exposure to a low dose atrazine metabolite mixture on pubertal timing and prostate development of male Long-Evans rats. *Reprod Toxicol* 30(4):540-549.

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Genetic and epigenetic mechanisms in liver tumors of oxazepam-exposed mice

NTP studies examining liver tumors from a previous study revealed insight into the mechanisms of carcinogenesis in mice exposed to oxazepam. Data suggest that formation of hepatocellular adenomas and carcinomas in the mice involved alteration of the Wnt signaling pathway, oxidative stress, and potential epigenetic alterations.

Citation: Lahousse SA, Hoenerhoff M, Collins J, Ton TV, Masinde T, Olson D, Reboloso Y, Koujitani T, Tomer KB, Hong HH, Bucher J, Sills RC. 2010. Gene expression and mutation assessment provide clues of genetic and epigenetic mechanisms in liver tumors of oxazepam-exposed mice. *Vet Pathol*; doi: 10.1177/0300985810390019 [Online 7 December 2010].

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Useful immunohistochemical markers of tumor differentiation

Several experimental and diagnostic examples were presented to illustrate the utility of immunohistochemistry (IHC) as a supplement to standard staining techniques.

IHC has been somewhat underutilized in the practice of toxic pathology, but can be a valuable tool for the evaluation of rodent neoplasms, both in a diagnostic and investigational role.

Experimentally, IHC can be employed to investigate the earliest changes in transformed tissues, identifying cellular changes not normally visible with standard hematoxylin and eosin staining.

Citation: Painter JT, Clayton NP, Herbert RA. 2010. Useful immunohistochemical markers of tumor differentiation. *Toxicol Pathol* 38(1):131-141.

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Arsenic, stem cells and the developmental basis of adult cancer

NTP researchers, in an invited review, looked at available studies on the effects of arsenic on the development of cancer.

A mouse transplacental model has been developed, where maternal exposure to inorganic arsenic either acts as a complete carcinogen or enhances carcinogenic response to other agents given subsequently in the offspring, producing tumors during adulthood.

Arsenic impacts human stem cell population dynamics *in vitro*, by blocking differentiation pathways, and arsenic impacts key, long-lived stem cell populations as critical targets to cause or facilitate later oncogenic events in adulthood as a possible mechanism of developmental basis of adult disease.

Citation: Tokar EJ, Qu W, Waalkes MP. 2010. Arsenic, stem cells and the developmental basis of adult cancer. *Toxicol Sci*; doi: 10.1093/toxsci/kfq342 [Online 11 November 2010].

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Cancer in experimental animals exposed to arsenic and arsenic compounds

NIEHS/NTP researchers reviewed the available rodent studies considered relevant to carcinogenic assessment of arsenic, discussing them in the context of the persistent argument that arsenic is not carcinogenic in animals.

It has proven difficult to provide experimental evidence of the carcinogenicity of inorganic arsenic in laboratory animals, but more recent work with arsenical methylation metabolites and early life exposures to inorganic arsenic has now provided evidence of carcinogenicity in rodents.

Given that tens of millions of people worldwide are exposed to potentially unhealthy levels of environmental arsenic, *in vivo* rodent models of arsenic carcinogenesis are a clear necessity for resolving critical issues.

Citation: Tokar EJ, Benbrahim-Tallaa L, Ward JM, Lunn R, Sams RL 2nd, Waalkes MP. 2010. Cancer in experimental animals exposed to arsenic and arsenic compounds. *Crit Rev Toxicol* 40(10):912-927.

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(Matt Goad is a contract writer with the NIEHS Office of Communications and Public Liaison.)

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Inside the Institute

NIEHS holds annual awards ceremony

By Melissa Kerr

NIEHS recognized employees' accomplishments at the 2010 NIEHS Awards Ceremony Dec. 16 in Rodbell Auditorium. The standing-room-only event was hosted by Paul Foster, Ph.D., NTP Toxicology Branch chief. NIEHS/NTP Director Linda Birnbaum, Ph.D, presented the record number of awards ([see program](#)).

In her opening statement, Birnbaum commended employees by saying, "I am pleased to have this opportunity to show you my gratitude for all that you have done to give of your talents and to share your knowledge, as we work together to improve human health around the world."

Before the formal ceremony began, Birnbaum presented an unannounced award to Steven Kleeberger, Ph.D., for his services as NIEHS acting deputy director while Birnbaum put together a permanent leadership team.

The awards honored employees for their contributions throughout the year at the Institute, including the NIEHS response to the Gulf oil spill with its training of thousands of cleanup workers, the initiation of a long-term health effects study, and continued support for the Gulf region research consortia. The establishment of the Breast Cancer and Environmental Research Coordinating Committee was another significant achievement of the year.

The program also recognized earlier awards to employees by the U.S. Department of Health and Human Services and NIH Director Francis Collins, M.D., Ph.D. Also honored were the 21 trainees who won this year's Fellows Award for Research Excellence (FARE), which came with a stipend of \$1,000 to go toward professional development.

After the ceremony concluded, attendees were invited to the cafeteria to celebrate International Day. The NIEHS band provided the holiday-inspired music as employees celebrated cultural diversity with fellowship and a remarkable variety of international cuisine.

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



Kleeberger, center, and Birnbaum share a hug and a laugh as he accepted a surprise award. Foster applauds in the background. (Photo courtesy of Steve McCaw)



Gina Goulding, left, receives a Peer Award from Birnbaum for her work on promotion procedures for laboratory staff. Peer Awardees were also awarded \$600 in cash. (Photo courtesy of Steve McCaw)



Jan Drake, Ph.D., accepts an NIH Merit Award from Birnbaum for exceptional leadership as the Chief of the Laboratory of Molecular Genetics over the past thirty years. (Photo courtesy of Steve McCaw)



Jai Tubbs enjoys the abundance of international flavors displayed prominently in the NIEHS cafeteria following the awards ceremony. (Photo courtesy of Steve McCaw)



Lysandra Castro and her daughter were among several attendees who wore traditional attire from some of the many cultures represented at NIEHS. (Photo courtesy of Steve McCaw)



First Environments day care students were home for a snow day, but several employees, including Michelle Campbell, above, brought along their children to share in the fun. (Photo courtesy of Steve McCaw)



A Germanic tradition fitting for International Day, this decorated fir tree helped reinforce the festive mood of the afternoon. (Photo courtesy of Steve McCaw)



Decked out in holiday red, NIEHS band members Gary Delaney and Dick Sloane helped set the holiday mood. (Photo courtesy of Steve McCaw)

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CFC has best year yet

By Eddy Ball

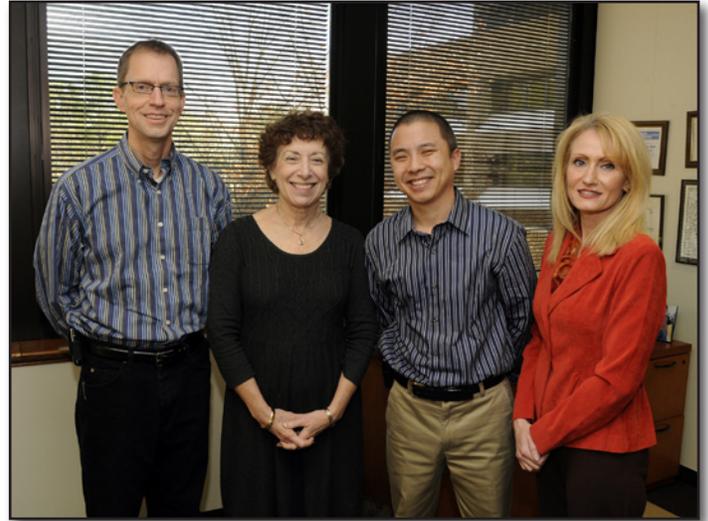
2010 was a banner year for NIEHS participation in the Combined Federal Campaign (CFC). Chaired by NIEHS Public Affairs Specialist Ed Kang, efforts by a small army of volunteers and a full schedule of events (see text box) inspired employees to pledge in record numbers and at record levels this year.

The statistics are impressive and the envy of other agencies across North Carolina, the NIH, and the nation:

- \$106,000 pledged — \$12,000 more than the previous record set in 2005, and \$15,000 or 15 percent greater than last year
- 206 participants — the highest overall number and percentage, at 30 percent, since 2005
- \$513 average pledge — including direct contributions by employees who cannot make payroll deductions

Looking back at the three months of planning, special events, and appeals, Kang said, “In my 10 years of federal employment, I’ve never seen this level of generosity and good will.” Kang said he was especially proud of the way NIEHS compares to other federal agencies. “Although we’re only 3 percent of the federal workforce of 20,000 employees in the Triangle and Triad, NIEHS represents about 12 percent of the overall fundraising.”

Kang added that the other NIH institutes and centers (ICs) in the Washington area have their own reasons to be envious. “At two weeks before deadline, we had already made our pledge goals for this year, something only four much smaller ICs could also boast of accomplishing,” he said.



With two weeks still left before the close of the 2010 CFC drive Dec. 15, it was already time to celebrate success. Shown above, left to right, are NIEHS Acting Associate Director for Management Chris Long, NIEHS/NTP Director Linda Birnbaum, Kang, and NIEHS Director of the Office of Communications and Public Liaison Christine Flowers. (Photo courtesy of Steve McCaw)



Food was a big part of the special events of this year's CFC pledge drive. Postdoctoral fellows Angelika Zaremba, left, and Tobias Schenk enjoyed themselves at an ice cream social. (Photo courtesy of Steve McCaw)

2010 CFC honor roll

Among the 205 participants who made pledges this year, several employees deserve special mention for their extra efforts to make the campaign a success. Along with their valuable services networking, these employees provided the organization and people power responsible for the drive's events and special features, including the CFC blog Web site, daily updates, charity fair, ice cream socials, raffles, and cafeteria tables.

Division Chairs — Elizabeth Ruben, Division of Extramural Research and Training; Eli Ney, Division of Intramural Research; Rachel Frawley, National Toxicology Program; Judy Hanson, Office of the Director; and Dona McNeill, Office of Management.

Keyworkers — Bonnie Allen, David Armstrong, Pat Barbour, Jeanie Jo Bell-Nichols, Danielle Carlin, Lysandra Castro, Shannon Duncan, Jenn Evans, Meg Fender, Barb Gittleman, Wes Gladwell, Gina Goulding, Christine Johnson, Pat Johnson, Gezell Jones, Denise Lasko, Leslie Lynch, Jacqui Marzec, Beth Miller, Suzy Osborne, Shyamal Peddada, Paul Poliachik, Dudley Riner, Debbie Wilson, and Diane Wilson.



And there was always a place for giveaways to help motivate pledges. Chairs and keyworkers demonstrated their solidarity at one of the many special events. Shown are J.J. Bell-Nichols, seated, and standing left to right, Jenn Evans, Kang, Meg Fender, Judy Hanson, and Eli Ney. (Photo courtesy of Steve McCaw)



As the holiday season approached, the NIEHS band offered its contribution to spark the spirit of giving. From left to right, trumpeter Mike Humble accompanied trombonists Doug Bristol and Dick Sloane as the band helped the audience give a toot about making 2010 a record year. (Photo courtesy of Steve McCaw)



A crowd gathered on the U.S. Environmental Protection Agency patio for the EPA-NIEHS Fun Run. Shown above, Chris Long, left, registered as division chair Rachel Frawley, seated, explained the route that runners would follow through the NIEHS-EPA campus. (Photo courtesy of Steve McCaw)



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