

October 2012

## NIEHS Spotlight



### [Directors report to council](#)

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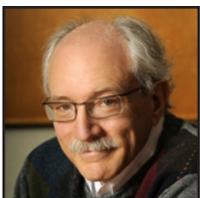
### [Former postdoc lands first NIH grant](#)

Former NIEHS trainee Rebecca Heise, Ph.D., has just completed the second big step of her academic career by becoming a co-lead researcher on a four-year NIH grant.



### [Moving forward with alternative test methods](#)

NIEHS hosted the annual meeting of the Scientific Advisory Committee on Alternative Toxicological Methods Sept. 5-6 in Research Triangle Park, N.C.



### [Woychik addresses environmental epidemiologists at 24th ISEE](#)

At the conference Aug. 26-30, NIEHS Deputy Director Richard Woychik, Ph.D., framed a future for environmental epidemiology based on the new NIEHS strategic plan.



### [Council approves SRP training concept](#)

At its Sept. 11 meeting, Council also gave an enthusiastic, unanimous green light to a concept presented by the Superfund Research Program.

## Science Notebook



### [Birnbaum talks science and strategy at Dioxin 2012](#)

NIEHS/NTP Director Linda Birnbaum, Ph.D., made three invited oral presentations and was lead researcher on four poster presentations at Dioxin 2012.



### [Models take spotlight at council science talks](#)

Advances in animal models were the focus of two scientific presentations at the Sept. 11 National Advisory Environmental Health Sciences Council meeting.



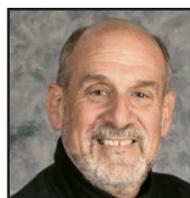
### [Mouse studies may help unravel human illnesses](#)

According to this month's NIEHS Distinguished Lecturer, mouse geneticist Monica Justice, Ph.D., studying mice can help scientists better understand human diseases.



### [Allergy research uncovers heart attack link](#)

The study by NIEHS researchers is the first to measure the presence of allergic antibodies in relation to past myocardial infarction in the U.S.



### [New strategy may improve delivery of medicines to the brain](#)

The experimental treatment method allows small therapeutic agents to safely cross the blood-brain barrier by turning off a key gatekeeper protein.

## NIEHS Spotlight



### [Flame retardant narrative shows why scientists need to communicate with policymakers](#) ▶ Video

Chemist and public health advocate Arlene Blum, Ph.D., visited NIEHS Sept. 18 to discuss “Flame Retardants and Public Health: How Science Can Inform Policy.”



### [NIEHS recognizes trainees on Postdoc Appreciation Day](#)

NIEHS joined institutions throughout the U.S. and Canada in recognition of National Postdoc Appreciation Week with a special celebration Sept. 21.



### [Stokes inducted as Board Certified Environmental Scientist](#) ▶ Video

NTP center director Rear Adm. William Stokes, D.V.M., was selected by the American Academy of Environmental Engineers as one of the inaugural 21-member class.



### [NIEHS fellow transitions from bench to field applications specialist](#)

Jill Hesse, Ph.D., left NIEHS this summer for a field applications specialist position at GenoLogics, a genomics laboratory information management system software company.



### [Dartmouth SRP mercury movie premieres on the big screen](#) ▶ Video

Reaching out to inform consumers about mercury in seafood, researchers screened a short NIEHS-funded film in Boston, Mass. and in two New Hampshire locations in September.

## Science Notebook



### [Epigenetic studies can shed light on causes underlying complex disease](#) ▶ Video

In a seminar Sept. 10 at NIEHS, grantee Robert Wright, M.D., explained the importance of epigenetics in reproductive health research.



### [Challenges persist in the critical task of determining safety of nanomaterials](#)

NIEHS participated in an expert workshop to address issues involved in setting occupational levels of exposure for nanomaterials.



### [Integrating learning and memory tests into developmental neurotox studies](#)

An enthusiastic audience of toxicologists and neuroscientists was on hand Sept. 6 to hear a presentation by animal behavioral testing expert Charles Vorhees, Ph.D.



### [Exploratory study first to quantify TCE in breast milk](#)

A new study funded in part by the NIEHS Superfund Research Program reports, for the first time, levels of the environmental contaminant trichloroethylene in breast milk.



### [Former Superfund trainee honored for mass spec research](#)

Food chemist and toxicologist Nils Schebb, Ph.D., was honored Sept. 18 for research he conducted as an NIEHS-supported postdoc at the University of California, Davis.

## NIEHS Spotlight



### [Sieber named to Amputee Coalition advisory committee](#)

NIEHS biologist Stella Sieber is one of three new members of the Amputee Coalition Scientific and Medical Advisory Committee.



### [“Silent Spring” turns 50](#)

Sept. 27 marked the 50th anniversary of the book credited with jump-starting the environmental movement, “Silent Spring” by marine biologist Rachel Carson.



### [NIEHS celebrates Labor Day with public health presentation](#)

Craig Slatin, Sc.D., placed contemporary labor and public health issues into historical context, as he built an argument for protecting workers and the environment.



### [Library staff in place and ready to assist](#)

With the hire of contract librarian Julie Harris in September, the NIEHS Library team now includes three full-time information professionals.



### [NRC report supports NIEHS vision of the exposome](#)

National Research Council report, “Exposure Science in the 21st Century: A Vision and A Strategy,” was released Sept. 7 by the National Academy of Sciences.

## Science Notebook



### [Paraoxonases — poster-children for gene-environment interactions](#)

Veteran NIEHS grantee Clement Furlong, Ph.D., spoke at NIEHS Sept. 4 on “The Many Facets of Gene-Environment Interactions of the Paraoxonases.”



### [Kunkel delivers keynote at Gordon conference on mutagenesis](#)

NIEHS scientists and grantees convened with internationally renowned scientists in Newport, R.I. for the 2012 Mutagenesis Gordon Research Conference.



### [Study finds that dad's job can influence birth defects](#)

A new NIEHS-funded study suggests men who work in certain occupations around the time of conception are more likely to father offspring with various birth defects.



### [Novel technique for determining DNA damage effects on gene transcription](#)

A new study funded in part by NIEHS may enhance researchers' ability to determine how a particular DNA lesion alters transcription and gene expression.



### [Low dose experts gather in Berlin](#)

NIEHS/NTP Director Linda Birnbaum, Ph.D., welcomed participants to an international workshop Sept. 11 in Berlin with a video presentation.



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

For its annual Children's Health issue, Environmental Health Perspectives highlights new research on how assisted reproduction and epigenetics impact development.

## Inside the Institute



### [NIEHS kicks off CFC and boosts pledge goal](#)

The great chili chefs of NIEHS were back on the job Sept. 18, as the Institute kicked off its 2012 Greater North Carolina Combined Federal Campaign drive.



### [Feds Feed Families drive underscores NIEHS generosity](#)

NIEHS staff donated 3,600 pounds of food and toiletries during the 2012 Feds Feeds Families campaign, beating its 2011 performance and its 2012 goal.



### [NIEHS honors dedication and longevity](#)

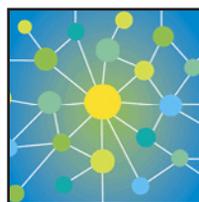
Continuing a long-standing tradition, NIEHS honored employees for their decades of service during a Sept. 13 ceremony.

## Science Notebook



### [Upcoming workshop on innovative safety tests for pertussis vaccines](#)

NIEHS and FDA scientists will join international experts this fall to consider improved methods and approaches for safety testing of whooping cough vaccines.



### [Workshop on human genomic plasticity begins Oct. 4](#)

There's still time to register for free onsite attendance and webcast access for this exciting exploration of emerging science for environmental health decisions.

## Extramural Research

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

- Triclosan impairs heart and skeletal muscle contractility
- Pan-fried red meat increases risk for prostate cancer
- Uncovering a defective gene's role in autism-type behaviors
- Infant exposure to specific molds linked with asthma risk

## Intramural Research

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

- Maternal smoking during pregnancy leads to modifications in child's DNA
- Novel protein limits programmed mutagenesis to antibody-producing genes
- Cerium dioxide nanoparticles may lead to human immune cell death
- Study dissects regulation of innate immunity by p53 tumor suppressor

## Calendar of Upcoming Events

- **Oct. 1-2**, in Rodbell Auditorium, Oct. 1, 1:00-5:00 p.m. and Oct. 2, 8:30 a.m.-5:00 p.m. — Peer Review of Draft NTP Monograph on Developmental Effects and Pregnancy Outcomes Associated with Cancer Chemotherapy Use during Pregnancy
- **Oct. 2**, in Rodbell C, 11:00 a.m.-12:00 p.m. — LMG Fellows' Invited Guest Lecture, with Kami Ahmed, Ph.D., speaking on "Genomic functions of H3.3 assembly factors"
- **Oct. 3**, in Rodbell Auditorium, 11:00 a.m.-12:00 p.m. — 2012 Hispanic Heritage Month, with Elizabeth Yeampierre, J.D., discussing "Intergenerational Leadership: The Foundation to Environmental Health and Sustainably Just Solutions"
- **Oct. 5**, in Rodbell Auditorium, 1:00-2:00 p.m. — Seminar featuring Gad Getz, Ph.D., addressing "Cancer Genomes Analysis: Computational Challenges and Approaches"
- **Oct. 11-12**, in Rodbell Auditorium, 8:30 a.m.-4:00 p.m. — WETP Workshop on Evaluation of Training
- **Oct. 15 (offsite event)**, at the U.S. Environmental Protection Agency in Research Triangle Park, N.C., 9:00 a.m.-4:00 p.m. — Symposium and Dialogue on Science, Risk Assessment, and Environmental Justice, [register](#)
- **Oct. 18 (offsite event)**, at the Bill and Ida Friday Center for Continuing Education in Chapel Hill, N.C. — Genetics and Environmental Mutagenesis Society annual fall meeting, [register](#)
- **Oct. 21-24, (offsite event)**, at the Marriot City Center in Raleigh, N.C. — 25th Annual Meeting of the Superfund Research Program, [register](#)
- **Nov. 1-2**, in Rodbell Auditorium, 8:30 a.m.-4:00 p.m. — NIEHS Science Days
- View More Events: [NIEHS Public Calendar](#)

# NIEHS Spotlight

## Directors report to council

By Ernie Hood

With all of its business conducted in one day instead of the usual two, the Sept. 11 [National Advisory Environmental Health Sciences Council](#) meeting was even busier than usual. The event featured updates from NIEHS/NTP Director Linda Birnbaum, Ph.D., and Division of Extramural Research and Training (DERT) Director Gwen Collman, Ph.D., as well as a Concept Clearance for a new Superfund Research Program (SRP) training initiative ([see related article](#)) and two scientific presentations on advanced biomedical research model systems ([see related article](#)).

In its closed afternoon session, Council also for the first time considered grant applications falling under the new NIH guidelines for Special Council Review. With some exceptions, all competing Research Project Grants with direct costs exceeding \$1 million — a change from the earlier NIH threshold of \$1.5 million in total costs — will be subject to the Special Council Review process.

### Putting the plan into action

Both Birnbaum and Collman addressed the status of implementation of the new [NIEHS 2013-2017 Strategic Plan](#), which was released August 1 after an 18-month development process.

“We’re currently working very hard on the implementation plans, which constitute exactly what we are going to do and how we are going to spend our money to do it over the next five years,” said Birnbaum. “The divisions have all developed individual implementation plans, which are now being merged into an institute-wide implementation plan, including cross-divisional efforts.... We now have a number of implementation teams forming across the Institute to look at some of the major issues that we will spend a lot of effort on in the next couple of years in the intramural program, the extramural program, and the Division of the National Toxicology Program as well.”



*Amid the ongoing budgetary uncertainties, Birnbaum maintains her upbeat demeanor, here enjoying a lighthearted moment with Council. As usual, she briefed the committee on the latest news and highlights at NIEHS. (Photo courtesy of Steve McCaw)*



*Collman also updated Council on the status of NIEHS extramural involvement in the FDA/NIH Tobacco Research Program. She noted that NIEHS is currently participating in several funding opportunities under the Family Smoking Prevention and Tobacco Control Act, the 2009 legislation that supports research into certain aspects of tobacco production and marketing. (Photo courtesy of Steve McCaw)*

Collman noted that DERT has been quite busy with Strategic Plan-related activities. “Much of our time, attention, and energy over the last months was taken up by a set of very interesting and exhilarating discussions about the Strategic Plan,” she told Council. “In DERT, we’ve created Strategic Goal implementation teams, and they’ve been quite active brainstorming ideas on the goal areas and coming up with a series of activities for the next five years. We’re now in the process of prioritizing, and soon will be matching those great ideas to budget realities.”

Birnbaum said that the implementation plans currently being developed should be in place by the next Council meeting in February 2013.

### **Budget uncertainty continues**

Along with her usual updates on NIEHS activities and scientific advances, Birnbaum described the current and near future budget situation for the Institute, the NIH, and the Federal government. “We all know that Congress is not going to pass a budget until at least after the election, and many people think that a budget may take much longer than that to actually happen,” she told Council members. The expectation, she said, is that there will be a new six-month Continuing Resolution (CR) in place by late September. She added that the budget-related planning going on at the NIH level is concerned with how the agency will go forward for the next six months under a new CR.

She also described the potential effects of sequestration, which would occur on January 3, 2013 if a budget agreement has not been made — the so-called going off the fiscal cliff scenario by activating automatic, deep cuts in federal spending.

The Department of Health and Human Services would be cut by approximately 8.2 percent, as would NIH and each of the its institutes and centers, including NIEHS. Birnbaum remains hopeful that cooler heads will prevail in Washington. “I think everyone is hoping very hard that once the election is over, people will get to work and make the appropriate decisions so that the automatic sequestration will not kick in, because it would be devastating to many, many programs in our country,” she said.

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



*Birnbaum presented the first of the four retiring Council members with a Certificates of Appreciation for her service. Shown above is Grace LeMasters, Ph.D., a professor of environmental health at the University of Cincinnati College of Medicine. (Photo courtesy of Steve McCaw)*



*Stephen Lloyd, Ph.D., a senior scientist and professor of genetics at the Oregon Health and Science University Center for Research on Occupational and Environmental Toxicology, was the next to be recognized. (Photo courtesy of Steve McCaw)*



*Birnbaum thanked Sem Phan, Ph.D., a professor of pathology at the University of Michigan Medical School. (Photo courtesy of Steve McCaw)*



*Palmer Taylor, Ph.D., a professor of pharmacology and associate vice chancellor for health sciences at the University of California, San Diego, received his plaque. (Photos courtesy of Steve McCaw)*

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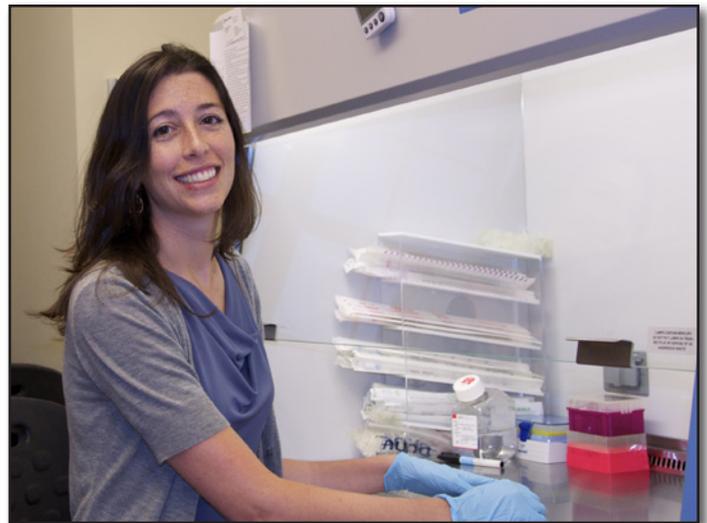
## Former postdoc lands first NIH grant

*By Eddy Ball*

Former NIEHS trainee Rebecca Heise, Ph.D., has just completed the second big step of her academic career by becoming a co-lead researcher on a four-year NIH grant.

In collaboration with two of her colleagues at Virginia Commonwealth University (VCU), Heise will use more than \$1 million in [funding](#) from the National Institute on Aging (NIA) to develop a multiscale hybrid mathematical model to help prevent ventilator-induced lung injury (VILI) — a line of research she had pursued in the lab of her NIEHS mentor, [Stavros Garantziotis, M.D.](#), Matrix Biology Group leader and Clinical Research Unit medical director.

“We want to try to understand how the cells in the lungs respond to the mechanical forces of breathing,” said Heise in a [VCU press release](#) about the award. “The purpose of the grant is to put different parameters of the math model together to help clinicians tailor ventilator settings for individual patients, to help prevent lung injuries that occur due to the ventilator.”



*NIA grantee Rebecca Heise shown in her lab at VCU (Photo by Lauren Hockaday, VCU School of Engineering media specialist)*

Heise, who left NIEHS in 2010 for a post at VCU, has a track record of beating the odds. She completed her Ph.D. in bioengineering in five years, she secured her position at VCU after just two years of postdoctoral fellowship training and, now, still in her early thirties, she's been awarded her first NIH research project grant, something most junior scientists usually don't achieve before they reach forty.

### Translational research that bridges disciplines

Heise holds dual undergraduate degrees in biomedical and chemical engineering from Carnegie Mellon University, and earned her Ph.D. in bioengineering from the University of Pittsburgh. Conducting basic research in molecular biology with Garantziotis' group helped her launch a line of research that promises positive therapeutic benefit for people at risk of experiencing complications from respiratory support.

In a 2010 Environmental Factor [article](#) by former NIEHS trainee Sophie Bullock, Ph.D., Heise explained that she had worked to understand the mechanisms by which lung cells sense and respond to mechanical strain. She feels this is an important area of research, because mechanical ventilation can cause or worsen lung injury, although respirator support can be crucial for a patient's survival. In some cases, VILI can even lead to respiratory failure and death.

Incidences of respiratory failure impacts approximately one in 3,000 U.S. residents, with mortality rates of approximately 40 percent. The majority of patients receiving mechanical ventilation are elderly patients whose respiratory systems fail to function due to various lung and airway diseases, such as acute respiratory distress syndrome and asthma — an important reason for Heise's choice of an aged mouse model for her experiments.

"Most people study young healthy animals and that's not very realistic, as most patients on ventilators are elderly," she said. "That's why we're looking at aged mice. We're looking at the response in the cells, the lung mechanics, and the inflammatory process in the whole animal."

### Capitalizing on the NIEHS training experience

During her time at NIEHS, Heise took full advantage of her lab experience with Garantziotis, as well as the many resources available from the [NIEHS Office of Fellows' Career Development \(OFCD\)](#) and [NIEHS Trainees Assembly \(NTA\)](#), including OFCD-sponsored career development workshops and the NTA-organized Biomedical Career Fair held each spring.

Working in a small lab allowed her to form close working relationships with her colleagues and benefit from focused mentoring by Garantziotis. In a message to him about her new grant, Heise thanked Garantziotis for his mentoring. "I certainly couldn't have written this grant without everything I learned from you," she wrote.

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*Garantziotis said of Heise's work at NIEHS, "She was able to build on skills she had developed as a Ph.D. student, while applying them in a different model. This [skill set] enabled her to have a running start, but also allowed her to claim novelty in her approach." (Photo courtesy of Steve McCaw)*

# Moving forward with alternative test methods

By Robin Mackar

Reflecting on past achievements, moving forward, and establishing good metrics were some of the key themes that emerged during the annual meeting of the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) Sept. 5-6 at NIEHS.

“ICCVAM has tripled progress in bringing alternative methods forward in the past five years,” said Rear Adm. William Stokes, D.V.M., as he provided the advisory committee with an update on the efforts of the 15-member Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), which his office, the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), supports. “We now have 58 alternative test methods that have been adopted and available for use, with 36 of those being *in vitro* tests that do not require animals.”

## ICCVAM successes

Stokes and other ICCVAM representatives elaborated on key accomplishments throughout the meeting, including progress in bringing 26 alternative methods forward for five of the six most commonly used tests to protect human health. If used, Stokes said, these tests could reduce animal use by 50 percent or more. ICCVAM has also contributed to the 14 alternative methods available for reducing and refining animal use for biologics and vaccine safety testing.

NTP associate director John Bucher, Ph.D., cited the maturation of the program over the years, during his welcoming remarks. He highlighted the creation of the [International Cooperation on Alternative Test Methods](#) as an example of what can happen when agencies and countries work together to integrate and harmonize approaches. “The result is a much more efficient process for the acceptance of alternative methods across the globe,” Bucher said. Representatives from the Republic of Korea, Japan, Canada, and the European Union were on hand at the meeting to present updates on their organizations’ efforts.

Warren Casey, Ph.D., deputy director of NICEATM, also presented new findings on a method recently recommended by ICCVAM, LUMI-CELL<sup>®</sup>, that has been specifically adapted for high-throughput or robotic toxicology testing by the National Center for Advancing Translational Sciences (NCATS). This method uses a human cell line, BG1, to identify potential endocrine disruptors without using animals. The NICEATM preliminary evaluation found that the high-throughput assay was as accurate as the manual one currently



Attending her last meeting of SACATM before her term expires, Gwendolyn McCormick, D.V.M., of Boehringer Ingelheim Pharmaceuticals Inc. provided input on how ICCVAM can better communicate its progress. (Photo courtesy of Michael Garske)



SACATM member Ochoa called for committee members to play a more active role in advising and assisting ICCVAM throughout the year. (Photo courtesy of Michael Garske)

being used, and could test many substances, at different doses, in a short period of time. Casey noted that the assay was developed by an NIEHS grantee supported, in part, through the Superfund Research Program (see text box).

### Other Federal efforts

Staff from NIEHS, NIH, and EPA also presented some interesting talks, as they highlighted new research areas that might be incorporated into ICCVAM's new strategic planning efforts. Margaret Sutherland, Ph.D., of NIH, spoke about the use of the NIH Common Fund to develop 3-D tissue models to help predict drug safety; NIEHS program administrator Daniel Shaughnessy, Ph.D., highlighted projects funded by NIEHS through the [Small Business Innovation Research program](#); and Mary Manibusan, of the EPA, provided an update on the Endocrine Disruptor Screening Program for the 21st Century.

ICCVAM Vice-chair Joanna Matheson, Ph.D., of the U.S. Consumer Product Safety Commission, followed up by describing the four key strategic opportunities and the ongoing transformation of safety testing presented in the NICEATM-ICCVAM five-year plan.

### Need for metrics

SACATM members, including Chair Steven Niemi, D.V.M., from Massachusetts General Hospital; Steven Hansen, D.V.M., from the American Society for the Prevention of Cruelty to Animals; Ricardo Ochoa, D.V.M., Ph.D., from Pre-Clinical Safety Inc.; and others, called for more metrics and quantifiable goals to determine the real impact that ICCVAM is making. "We need to start counting our accomplishments in measurable ways, as soon as possible," Niemi said. He and others requested that ICCVAM find ways to determine baseline use of animals in safety testing and research so, a year from now, they can determine the progress made. They also called for regulatory agencies to start actively promoting the alternative methods that ICCVAM has already brought forward.

## Superfund research plays key role in cell bioassay development

Recent approval of an alternative cell bioassay for endocrine disruptors by the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) highlights a success story in translating basic research findings to worldwide applications.

This assay, called the LUMI-CELL<sup>®</sup> ER or BG1Luc estrogen receptor transactivation assay (BG1LucER TA) can now be used with confidence by governments around the world as a test for endocrine disruptors in various types of samples. The history of the assay development sheds light on how basic research at the Superfund Research Program (SRP) leads to successful development of products and outcomes that impact environmental health.

In the mid-1990s, there was a critical need for rapid, inexpensive, and high-throughput methods for detection of endocrine disruptors, primarily xenoestrogens, that could be used as future screening assays by the U.S. Environmental Protection Agency (EPA). With funding from an SRP grant to the University of California, Davis, Michael Denison, Ph.D., and Jane Rogers, Ph.D., took advantage of the receptor-dependent mechanism of estrogen action to produce a recombinant human ovarian carcinoma (BG1) cell line, referred to as BG1Luc4E2 cells, to meet this need.

The recombinant cells contain a stably transfected estrogen-responsive firefly luciferase reporter gene that responds to estrogenic chemicals by inducing luciferase activity in a time-, dose-, chemical-, and estrogen receptor-dependent manner. This new bioassay is rapid, inexpensive, and sensitive. Most importantly, it provides a new screening bioassay for activators and inhibitors of the estrogen-receptor signaling pathway.

This research led to a subsequent collaboration between a small biotechnology company, Xenobiotic Detection Systems, and Denison to further develop and optimize the bioassay for commercial screening purposes. ICCVAM made its recommendation in 2012 ([see story](#)), and the assay is now being used by the U.S. EPA, NTP, and in screening of the Tox21 10K library.

For additional information, see studies by Denison and Rogers published in [2000](#) and [2002](#).



*Stokes noted the many achievements of ICCVAM over the past 15 years, during the SACATM meeting. (Photo courtesy of Michael Garske)*



*SACATM chair Niemi listened closely to all the discussions that occurred at the annual meeting. He and others called for more metrics to evaluate ICCVAM's progress in reducing, refining, and replacing animals in chemical and product safety testing. (Photo courtesy of Michael Garske)*



*NIH's Sutherland succinctly described an interesting project to develop microchips that can behave like human organs to help predict drug safety. The NIH Common Fund's Regulatory Science program is a partnership of NIH, the U.S. Food and Drug Administration, and the Defense Advanced Research Projects Agency, designed to advance the field of regulatory science. (Photo courtesy of Michael Garske)*



*Lori White, Ph.D., left, serves as the NTP Designated Federal Officer for SACTAM meetings. She and Bucher discussed how the meeting was proceeding, during a break. White was publicly commended by Joy Cavagnaro, Ph.D., of Access BIO, during Cavagnaro's presentation as chair of the Implementation Working Group, which looked into how ICCVAM methods are being implemented at agencies and research organizations. (Photo courtesy of Michael Garske)*



*Bucher and Stokes surprised ICCVAM Chair Jodie Kulpa-Eddy, D.V.M., of the U.S. Department of Agriculture (USDA), with a plaque, certificates of appreciation, and flowers for her exceptional work with ICCVAM over the years. Kulpa-Eddy is ending her tenure on ICCVAM and will be taking on new responsibilities at USDA. (Photo courtesy of Michael Garske)*

(Robin Mackar is the news director in the NIEHS Office of Communications and Public Liaison.)

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## **Woychik addresses environmental epidemiologists at 24th ISEE**

*By Ed Kang*

At the International Society for Environmental Epidemiology (**ISEE**) conference Aug. 26-30, NIEHS Deputy Director Richard Woychik, Ph.D., framed a future for environmental epidemiology, in light of the newly released NIEHS [strategic plan](#). His plenary presentation, “Planning the Future: Strategic Directions for NIEHS and the Environmental Health Sciences Community,” outlined critical linkages between the future of NIEHS and the role of the environmental health researchers who were gathered in Columbia, S.C., to hear the latest in exposure assessment, methodologies, and gene-environment interactions.

Woychik’s keynote speech addressed not only interdisciplinary and international research, but also emerging global environmental health issues. “NIEHS will prioritize and assign resources and funding to make this plan come alive,” he said.

His keynote presentation was part of a substantial NIEHS presence at the meeting. In addition to Woychik, conference attendees were also able to hear from numerous NIEHS extramural program administrators, grantees, and intramural scientists.

According to NIEHS Division of Extramural Research and Training (DERT) Director Gwen Collman, Ph.D., “The meeting gave NIEHS scientists and grantees extraordinary opportunities for networking and exploring international and cross-disciplinary partnerships.”

Representatives from the extramural division led several important seminars. Collman was a key speaker on multiple panels addressing data sharing initiatives and concerns, while Health Scientist Administrator Caroline Dilworth, Ph.D., who co-directs the extramural environmental epidemiology program, helped provide guidance to new and rising researchers on how to navigate the NIH funding system. Claudia Thompson, Ph.D., Susceptibility and Population Health Branch chief, brought her expertise on community-based participatory research to several discussions on science and policy best practices.

NIEHS Epidemiology Branch Chief, Dale Sandler, Ph.D., led several discussions on research in the context of environmental disasters, using the Gulf oil spill research efforts as a framework.

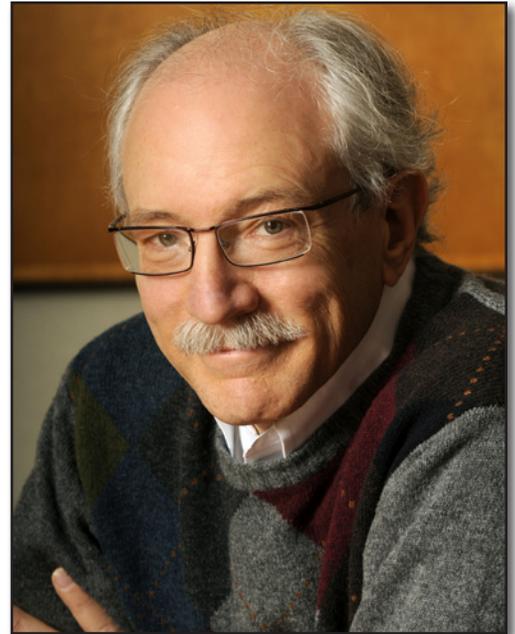
### **NIEHS grantees take top honors**

Two high-profile NIEHS grantees were awarded top honors for their outstanding and sustained efforts in the field. Brenda Eskenazi, Ph.D., from the University of California, Berkeley School of Public Health received the John Goldsmith Award for Outstanding Contributions to Environmental Epidemiology. Additionally, Bruce Lanphear, M.D., is this year’s ISEE Research Integrity Award winner. Lanphear is a clinician-scientist at the Child and Family Research Institute at British Columbia Children’s Hospital and a professor at Simon Fraser University in Vancouver.

NIEHS provided financial sponsorship for the meeting, which drew researchers from around the world to an extensive program cleverly organized around themes of land, sea, and air. Next year’s conference will focus on the group’s quarter-century milestone and will be held in Basel, Switzerland.

(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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*“There’s a part for each one of you [in the strategic plan],” Woychik said to the gathering of about 700, representing the epidemiology, exposure assessment, toxicology, biochemistry, and biostatistics fields. (Photo courtesy of Steve McCaw)*



*Collman, center, is pictured with 2012 ISEE award winners and NIEHS grantees, Lanphear, left, and Eskenazi. DERT was well represented at this year’s meeting, with Collman leading the planning activities as co-chair of the ISEE Scientific Program Committee. (Photo courtesy of Ed Kang)*

# Council approves SRP training concept

By Ernie Hood

At its Sept. 11 meeting, Council also gave an enthusiastic, unanimous green light to a concept presented by the Superfund Research Program (SRP). Following up on the responses received after a Request for Information (RFI) issued in February, the SRP requested Council's approval to proceed with an initiative called Occupational Safety and Hazardous Substances Training Programs in Emerging Technologies.

"We are one of the leaders in the area of supporting emerging technologies such as nanotechnology, exposure biology, green chemistry, sustainable remediation, and innovative hazardous waste processes," said SRP Director William Suk, Ph.D. "There needs to be a better understanding of what the health and safety measures are with regard to some of these emerging technologies."

Suk noted that there are currently very few educational programs for educating and training people in the universities or in real world positions about the potential health and safety problems associated with the advanced technologies.

The concept, which was presented to Council by SRP Program Administrator Danielle Carlin, Ph.D., would use the Research Education Program Grants R25 funding mechanism to support as many as four programs for up to three years, comprising \$750,000 per year in financial support.

Suk said that the program is designed to be translational in a very specific bidirectional pattern. "The idea is to be able to take the technologies and understand not just how they work, but what potential health problems might be associated with them. Also, we want to work with the people who are looking at health and safety issues in general, and say, 'Can we make this particular technology safer, but at the same time not lose its efficiency and its ability to reduce costs?'"

Council reviewers were Elizabeth Yeampierre, J.D., executive director of UPROSE, Brooklyn's oldest Latino community-based organization; and Howard Hu, M.D., who serves as director, dean, and professor with the Dalla Lana School of Public Health at the University of Toronto.



Carlin noted that the establishment of consortia with other institutions to achieve greater representation of various disciplines would be an integral element of the planned training program. (Photo courtesy of Steve McCaw)



Yeampierre, above right, and Hu, speaking by telephone, expressed their whole-hearted endorsement of the concept. (Photo courtesy of Steve McCaw)



According to Suk, the SRP has been supporting innovative technologies to enable science-based decision making. "The idea is that you can actually use some of these tools and technologies to make informed decisions with regard to risk, or with regard to clean-up," he noted. (Photo courtesy of Steve McCaw)

Applications for the program will be due in early 2013, with awards expected to be issued in June, 2013.

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

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## Flame retardant narrative shows why scientists need to communicate with policymakers

By Brant Hamel

According to chemist, public health advocate, and NIEHS guest lecturer Arlene Blum, Ph.D., North Americans live in a world awash with flame retardants, including the furniture they sit on, the baby and infant products they purchase, the air they breathe, and the material they use to insulate their houses. Flame retardants are even present in household dust on the floors where children and pets spend so much of their time.

Blum visited NIEHS Sept. 18 to discuss “Flame Retardants and Public Health: How Science Can Inform Policy.” Blum is the executive director of the [Green Science Policy Institute](#) and a visiting professor of chemistry at University of California (UC), Berkeley, as well as a noted mountaineer and author. Blum’s talk was hosted by Linda Birnbaum Ph.D., director of NIEHS/NTP, who has also conducted extensive research into the negative health effects of flame retardants.



*Despite the grim scenario she painted about exposure to flame retardant chemicals, Blum is optimistic about the future. “When scientists make a strong statement,” she said, “things begin to happen.” (Photo courtesy of Steve McCaw)*



*Blum’s talk drew a diverse crowd, including lead researcher David Armstrong, Ph.D., right, who studies the effects of endocrine disrupting chemicals on the nervous system, and Sheila Newton, Ph.D., director of the Office of Policy, Planning, and Evaluation. (Photo courtesy of Steve McCaw)*

 **Linked video:**  
[Watch Blum’s video introduction to flame retardants \(15:53\)](#)  
(Launches in new window)

Download Media Player:  Flash 

Given the ubiquitous use of these chemicals, people hope that they serve to protect from the dangers of fire with no unnecessary health risks. However, as Blum told the audience at NIEHS, although scientists have convincingly shown that flame retardants are not safe or very effective, researchers still need to effectively communicate their findings to the policymakers who set standards for the use of these chemicals. “But the good news,” she told her audience, “is that this is a problem we can solve.”

## Tris returns — a bad actor that keeps questionable company

Blum obtained her doctorate in biophysical chemistry at UC Berkeley and went on to conduct pioneering work with renowned biochemist Bruce Ames, Ph.D., on the health effects of brominated Tris flame retardants that during the mid-1970s constituted up to 10 percent of the weight of children’s pajamas. After showing that brominated Tris was extremely mutagenic and could be identified in a child’s blood following a single night of sleep, in 1977, the U. S. Consumer Product Safety Commission banned use of the product in children’s clothing. However, in what would be a common theme throughout Blum’s talk, industry replaced brominated Tris with another flame retardant, chlorinated Tris, which was also later removed from use in children’s clothing.

“The sad news is,” Blum said, “today chlorinated Tris is back. It’s in our furniture foam, it’s in baby products, at levels up to 10 percent the weight of foam.” The reason, she said, is the action of policymakers who adopted chemical industry-backed regulations, such as [flammability standard] TB 117 in California.

## Scientists should be proactive

Despite more than 3,900 peer-reviewed scientific papers documenting the negative effects of flame retardants, many policymakers are still not aware of adverse health effects. Blum argued that scientists not only can, but should, inform policy and need to proactively seek out and engage policymakers.

To illustrate how scientists can make a difference, Blum gave the example of a scientist who tracked down and spoke with the main policymaker responsible for setting flammability standards for furniture in the UK. As a result of his interaction with the scientist, the policymaker is now considering how to change the regulations.

Blum concluded by saying that it’s critical to drive more research to better understand the health effects of flame retardants and more effectively communicate the results to policymakers so that harmful chemicals can be eliminated from future products. Recent articles published in the [NY Times](#) and [Chicago Tribune](#) have highlighted Blum’s quest and her efforts to do her part to impact public health policy.

(Brant Hamel, Ph.D., is an Intramural Research Training Award fellow in the NIEHS Laboratory of Signal Transduction.)

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*During the question and answer segment of the presentation, NTP toxicologist Mike DeVito, Ph.D., expressed concern about the feasibility of submitting flame retardant chemicals to the gold standard of animal studies, which can take five years, he said. (Photo courtesy of Steve McCaw)*



*Birnbaum joined Blum at the podium and fielded several of the questions from the audience. (Photo courtesy of Steve McCaw)*

# NIEHS recognizes trainees on Postdoc Appreciation Day

By Eddy Ball

NIEHS joined institutions throughout the U.S. and Canada in recognition of [National Postdoc Appreciation Week](#) with a special celebration Sept. 21. The [NIEHS Trainees' Assembly \(NTA\)](#) held its fall General Assembly in Rodbell Auditorium, followed by an ice cream social and trivia games in the NIEHS cafeteria.

Moderated by steering committee co-chairs [Anne Marie Jukic, Ph.D.](#), and [Rachel Goldsmith, Ph.D.](#), who described events and opportunities sponsored by the NTA, the event featured talks about career skills training programs and trainee-related developments by NIEHS Scientific Director [Darryl Zeldin, M.D.](#), Division of the NTP (DNTP) Director [John Bucher, Ph.D.](#), and [Office of Fellows Career Development \(OFCD\)](#) Director [Tammy Collins, Ph.D.](#)

The program offered trainees an opportunity to understand better their place in the larger contexts of NIH, the NIEHS Divisions of Intramural Research (DIR) and NTP, and the NIEHS strategic plan, which promises to help shape the environmental health sciences worldwide over the next five years. The event was also a chance for senior researchers to explicitly remind trainees of their importance to the overall missions of NIH and NIEHS/NTP.

“We do love you,” said Zeldin at the beginning of his presentation. “You are the backbone of the Institute.”

## Looking at the big picture

Zeldin moved into a discussion of the importance of training goals in the NIEHS strategic plan, as it relates to enhanced teaching, promotion of scientific literacy, training diversity, and development of the next generation of biomedical researchers. His discussion of budget uncertainties and continuing reduction in terms of budget and training programs was sobering, but Zeldin also had encouraging news for trainees.

Promising developments listed by Zeldin included expansion of the minority Intramural Research Training Award Program, the proposed merit increase for postdocs who are awarded career transition grants, international joint training programs, and the new Fellow of the Year travel award.

Jukic introduced the members of the NTA steering committee who facilitate the group's input into such NIEHS decisions as hiring, working conditions, and the trainee renewal process. The members represent trainees in the various DIR labs and NTP branches and together perform an important role in advocating for their needs and articulating their interests.



*Co-chair Jukic opened the meeting and made the NTA steering committee report. (Photo courtesy of Steve McCaw)*



*Co-chair Goldsmith introduced Bucher, wrote up the trivia scores, and helped out with some logistics. (Photo courtesy of Steve McCaw)*

The NTA, Jukic reminded the audience, sponsors social and career development events, including coffee hours, lunches with distinguished lecturers, workshops, brown bag lunches, and the enormously popular annual Biomedical Career Fair, now in its 16th year, which will be held April 27, 2013. The NTA also helps fellows recognize outstanding lead researchers by selecting the Mentor of the Year honor each year on Science Day in November and publicizes volunteer career development opportunities that include writing for the [Environmental Factor newsletter](#) and working with the Citizen Schools and NIEHS Scholars Connect programs offered through the NIEHS [Office of Science Education and Diversity](#).

Collins, a former postdoc at NIEHS ([see story](#)), addressed the assembly for the first time in her new role leading OFCD. She explained the role of her office in coordinating [NIH Office of Intramural Training and Education \(OITE\)](#) resources for trainees at NIEHS and implementing NIEHS-based programs, such as upcoming workshops in 2012-2013 in graphic design, grant writing, spoken English, time management, teaching college, and drug development.

As the DIR clearinghouse for information about jobs, career development resources, and training opportunities, OFCD sends out regular emails through its fellows' listserv. Collins encouraged fellows to contact her with questions and concerns or to request a meeting.

Bucher closed out the program with a description of [NTP postdoctoral training opportunities](#), led by DNTP Director of Toxicology Training and Coordination [Rajendra Chhabra, Ph.D.](#) NTP training focuses on the kind of team science careers found in government and industry, Bucher said, rather than on lead researcher positions in academic settings.

While NTP has a few postdocs in its wet lab, he said, most of the positions are in pathology training, which leads to board certification in veterinary pathology, and in applied toxicology with an emphasis on study design and literature evaluation.

## A four-year tradition at NIEHS

National Postdoc Appreciation Day at NIEHS is the high point of National Postdoc Appreciation Week. The celebration was initiated in 2009 by the [National Postdoctoral Association \(NPA\)](#), a member-driven organization that provides a unique voice for postdoctoral scholars throughout the country. With its historically strong ties to NPA, NIEHS has been a part of the national movement from the beginning.

In 2010, this week was officially recognized by the U.S. House of Representatives with House Resolution 1515. In 2011, 89 institutions in 30 states and Canada hosted 171 events to show their appreciation of postdocs. In North Carolina this year, NIEHS, the University of North Carolina-Chapel Hill, and Wake Forest University held celebrations Sept. 17-21 recognizing the significant contributions that postdoctoral scholars make to U.S. research and discovery.

See related stories about Postdoc Appreciation Day at NIEHS in [2009](#), [2010](#), and [2011](#).



*Although he is concerned about budget uncertainty, Zeldin was upbeat about efforts to expand training opportunities at NIEHS. (Photo courtesy of Steve McCaw)*



*Collins presented a full schedule of OFCD confirmed and planned training opportunities for the next academic year; among them MOMDADDOCS, a program for trainees who are also parents. At the last NTA general assembly in April, she spoke as chair of the NTA steering committee. (Photo courtesy of Steve McCaw)*



*NTP has about ten percent the number of postdocs, and in most cases, as Bucher explained, their training experiences and career trajectories are different, reflecting the distinctive mission of NTP. (Photo courtesy of Steve McCaw)*



*As the trainees made clear, the competition was good-natured, as teams tried to outscore each other. Shown above, left to right, are Jim Aloor, Ph.D., Kym Gowdy, Ph.D., and Miranda Bernhardt, Ph.D. (Photo courtesy of Steve McCaw)*



*Xiaoling Li, Ph.D., was one of several lead researchers who joined trainees for refreshments and trivia games following the general assembly meeting. (Photo courtesy of Steve McCaw)*



*Even the last place team members had no trouble laughing at their defeat. The awards included ones for the winning team, as well as for Most Environmental Team Name, the Most Scientific Team Name, and the Most Humorous Team Name. (Photo courtesy of Steve McCaw)*



*Trainees gathered on the NIEHS patio for their traditional group photo, kicking off the new academic year. (Photo courtesy of Steve McCaw)*

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## Stokes inducted as Board Certified Environmental Scientist

*By Eddy Ball*

NTP center director Rear Adm. [William Stokes, D.V.M.](#), was selected as one of the inaugural 21-member class of Board Certified Environmental Scientists (BCESs). The announcement appeared in *Environmental Engineer*, the quarterly publication of the American Academy of Environmental Engineers (AAEE), which bestows the prestigious certification on environmental professionals.

“These highly qualified individuals were accepted into the Academy by unanimous vote during our spring Board of Trustees’ meeting,” wrote AAEE Immediate Past President Brian Flynn. “Their admission signals the beginning of our process to recognize the distinct and vital talents of environmental professionals: engineers and scientists working together to protect the environment today and our legacy tomorrow.”



**Linked video:**  
[Watch as Flynn discusses the new certification and awards the first BCES plaque \(01:28\)](#)

(Launches in new window)

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Stokes serves as director of the [NTP Interagency Center for the Evaluation of Alternative Toxicological Methods](#) and executive director of the [Interagency Coordinating Committee on the Validation of Alternative Methods](#), which provide scientific support and coordinate interagency initiatives for advancing new safety testing methods, including those that can replace, reduce, and refine the use of animals in toxicity testing. In addition to his AAEE certification, Stokes holds certification as a Diplomate of the American College of Laboratory Animal Medicine. He studied environmental and biomedical engineering at the University of Louisville’s J.B. Speed Scientific School, before attending the College of Veterinary Medicine at Ohio State University.

“This honor reflects well on Bill’s achievements in environmental public health and the promotion of alternative testing methods,” said NIEHS/NTP Director Linda Birnbaum, Ph.D. “I am gratified to see that his accomplishments are being recognized by his selection as a member of the first group of BCESs.”

### A new kind of certification

The BCES certification represents a broadening by AAEE in the range of its validation services. The idea of expanding the Academy’s certification mission to include environmental scientists arose from discussions in the early spring of 2010, which led to its implementation in November 2011. AAEE certifications are internationally recognized as premium credentials that are awarded to experienced professionals who have demonstrated expertise in one or more areas of specialization.

The basic premise was that, since most of the organizations that employ Academy members utilize environmental engineers and environmental scientists on multidisciplinary teams to solve environmental problems, it would be useful for AAEE to certify both. In this way, the Academy can offer the users of environmental services and environmental employers a full range of professional certification services.

The inaugural class of BCESs reflects the range of members — scientists working in the academic, government, foundation, and private sectors as biologists, chemists, geologists, hydrologists, and toxicologists — dedicated to protecting environmental public health. Stokes, who is the only veterinarian, and U.S. Environmental Protection Agency toxicologist Bruce Macler, Ph.D., are sole federal scientists in the new class of BCESs.

Like their engineering colleagues, BCESs must have at least eight years of professional experience and demonstrate high ethical integrity, before they can be considered as candidates by the AAEE Admissions Committee. Following approval as a candidate, in most cases, an aspiring board-certified environmental professional must stand for written and oral examinations.

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## NIEHS fellow transitions from bench to field applications specialist

*By Nisha Cavanaugh*

Postdoctoral fellow Jill Hesse, Ph.D., left NIEHS this summer for a field applications specialist position at [GenoLogics](#), a genomics laboratory information management system software company. Her new position will call upon her extensive knowledge of bioinformatics, communication skills, and experience as a detail-oriented bench scientist.



*Stokes is the sole member of the U.S. Public Health Service to become a BCES. (Photo courtesy of Steve McCaw)*

An Intramural Research and Training Award fellow in the NIEHS Environmental Stress and Cancer Group, Hesse worked with lead researcher [Richard Paules, Ph.D.](#), on ataxia telangiectasia mutated (ATM) kinase, an enzyme recruited and activated by double-strand breaks in DNA. Her research focused on the role ATM-dependent microRNAs play in the damage response to environmental exposure and, potentially, in predisposition to cancer. As Paules explained, “[Hesse] incorporated microarray analyses of messenger RNAs and microRNAs in her studies and was one of the first to run a microRNA next-gen sequencing project with NISC [the NIH Intramural Sequencing Center].”

In her new position, Hesse will be responsible for achieving expert-level knowledge of GenoLogics software capabilities and applications, sharing this knowledge and best training practices with customers worldwide, and contributing to the development of proposals and project plans. “I wanted to find a position that played to my strengths in communication and training, but where I still get to talk about science,” she said of her fit with the new position.

### **Combination of bench work and leadership roles diversified Hesse’s skills**

Hesse attributed getting the job to the training she received at NIEHS. Her research project gave her the opportunity to develop bioinformatics skills that will be crucial in her new position inside a software company. As Paules explained, “[Hesse] developed considerable expertise in bioinformatics and genomic database manipulations, in order to interpret her results. ... [This] was integral in making her an attractive candidate for the position.”

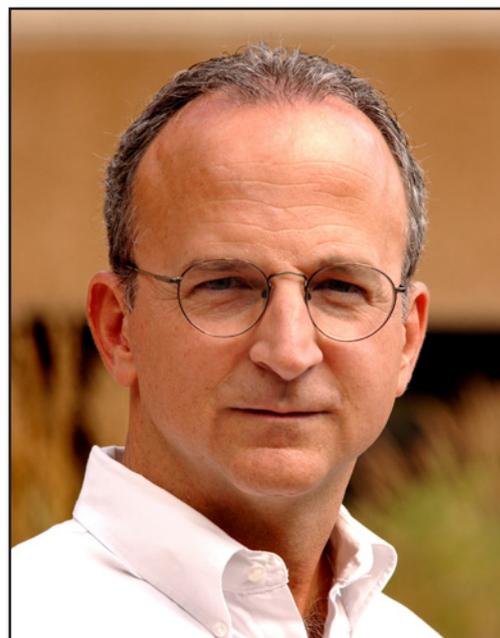
Additionally, Hesse took advantage of the Office of Fellows’ Career Development (OFCD) and the NIEHS Trainees Assembly (NTA) Steering Committee. The OFCD offered her opportunities to create a resume and practice interviewing skills, in addition to exposing her to a variety of Ph.D. careers.

As an active member of the NTA Steering Committee, Hesse served as a liaison with several groups at NIEHS, including the NIEHS leadership, Assembly of Scientists, and the Assembly of Laboratory Staff, to advocate for postdocs and maintain open lines of communication. Through her involvement with the NTA, she honed many of her transferable skills, including leadership, project management, communications, mentorship, and networking.

“I think networking is critical to anyone in a job search or who wants further development of his or her career,” Hesse noted. “Many people get job offers directly through networking but, even if you don’t, it is an invaluable opportunity to gain knowledge and confidence.”



*Hesse credits a recruitment group with helping her get a foot in the door. (Photo courtesy of Steve McCaw)*



*Working with the Paules group helped Hesse get valuable experience with leading-edge microarray and next-generation sequencing platforms. (Photo courtesy of Steve McCaw)*

## A job search road less traveled

When Hesse applied for the position at GenoLogics, she was automatically listed on a recruiter’s website and worked with a recruiter at [AchieveBio](#), a specialized search firm dedicated to providing top talent to the biotech and life science industries. While some job seekers may avoid this route, Hesse found working with a recruiter to be a valuable and positive experience, and she referred to it as advanced networking. In the initial meeting, the recruiter assessed how well Hesse would fit the position, based on her qualifications and her personality. Despite lacking any previous sales experience, the recruiter determined Hesse to be a good candidate for the position, and pushed her application forward. The recruiter also provided interview preparation support and feedback at every stage of the process.

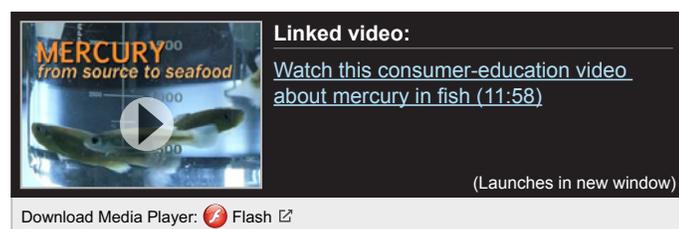
(Nisha Cavanaugh, Ph.D., is a postdoctoral fellow in the NIEHS DNA Repair and Nucleic Enzymology Group.)

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## Dartmouth SRP mercury movie premieres on the big screen

By Sara Mishamandani

Reaching out to inform consumers about mercury in seafood, the NIEHS-funded [Dartmouth Toxic Metals Superfund Research Program \(SRP\)](#) and the Geisel School of Medicine at Dartmouth screened a short film in Boston and at two New Hampshire locations in September. The video “Mercury: From Source to Seafood,” created by the Dartmouth SRP, describes the health effects of mercury in seafood and simplifies the complexities surrounding seafood consumption.



“This mercury film is the second in a short series of videos we felt would be an excellent way to put our science to use to help people with everyday issues that affect their health,” says [Bruce Stanton, Ph.D.](#), director of the toxic metals program and a professor at Geisel. “Consumers need to know why they should still eat fish, understand why mercury is in our seafood, and learn what we can do to prevent mercury from entering our environment. This movie tells the story in a compelling, but brief, format.”



*Celia Chen, Ph.D., introduced the video at Red River Theatres in Concord. Chen is featured in the film for her work on the fate of mercury in aquatic food webs. (Photo courtesy of Jared Rardin)*

## Mercury — from source to host

The 10-minute video follows the journey of mercury from coal-fired power plants to the seafood we eat. It discusses which species of fish contain the least and most mercury, and explains the possible adverse health effects of consuming high-mercury fish, particularly for pregnant women and young children. The film also describes the health benefits of eating low-mercury fish and the importance of reducing the amount of mercury that enters the environment.

The film premiered on the big screen Sept. 5 at the Dartmouth-Hitchcock Medical Center in Lebanon, N.H. The screening was followed by a panel discussion, to answer questions and further discuss the topic. The panel included [Celia Chen, Ph.D.](#), SRP research translation core leader and research professor in Dartmouth's department of biological sciences, and [Duane Compton, Ph.D.](#), senior associate dean of research at the Geisel School and a longtime biochemistry researcher.

The film was also screened at the Harvard School of Public Health in Boston and at the Red River Theatres in Concord, N.H., with panel discussions following the screening at both locations.

“I have been studying mercury in the environment for many years, and I am particularly pleased that this movie takes the confusion and mystery out of whether people should eat seafood,” said Chen. “While it is important to have the health benefits of eating fish, everyone needs to know which fish are safe to eat.”

The mercury film is the second in a series of videos created by the Dartmouth SRP to translate its relevant toxic metal research to the public. In 2010, the Dartmouth SRP produced the first video in the series, “[In Small Doses: Arsenic](#).” The film explained the risk associated with exposure to arsenic in private wells and the need to test for harmful levels of arsenic in well water.

Chen also publicized the video, and explained issues surrounding seafood consumption and mercury on two radio shows in New Hampshire in mid-September. She was featured on [New Hampshire Public Radio](#) and on the Arnie Arnesen Radio Show on WNHN radio in Concord.

(Sara Mishamandani is a research and communication specialist for MDB, Inc., a contractor for the NIEHS Superfund Research Program, Worker Education and Training Program, and Division of Extramural Research and Training.)

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*Community members received information on mercury in seafood before the video screening and panel discussion. (Photo courtesy of Jared Rardin)*



*Michael Paul, J.D., the Dartmouth SRP community engagement coordinator, spoke with viewers after the screening. (Photo courtesy of Jared Rardin)*

# Sieber named to Amputee Coalition advisory committee

By Eddy Ball

NIEHS biologist Stella Sieber is one of three new members of the Amputee Coalition Scientific and Medical Advisory Committee (SciMAC). In a [press release](#) issued Aug. 24, the group announced that Sieber will serve as a consumer representative.



The [Amputee Coalition](#), headquartered in Manassas, Va., is a national nonprofit organization dedicated to reaching out to and empowering people affected by limb loss to achieve their full potential through education, support, and advocacy, as well as to promote limb loss prevention ([see text box](#)). SciMAC serves as a resource to the organization, by contributing clinical and scientific expertise in the development, implementation, and evaluation of Coalition programs, research, and policy initiatives.

“It is my sincere hope that as part of the SciMAC we can improve the lives of amputees by informing, educating, supporting, and empowering them and their healthcare teams to lead healthy and productive lives,” Sieber was quoted as saying in the announcement of her selection.

## Pursuing a rich life of work, recreation, and service

Following extensive injuries from an automobile accident in 2001, Sieber learned to adapt to the loss of both of her legs, through a comprehensive rehabilitation program, continuing her productive work life at NIEHS, pursuing her extracurricular interests, and reaching out to other amputees.

Sieber is a biological science laboratory technician in the NIEHS Laboratory of Toxicology and Pharmacology Microarray Group, which supports gene expression studies in NIEHS labs. She is a founding member of the steering committee of the NIEHS Assembly of Laboratory Staff, the only NIH group of its kind devoted exclusively to communicating the interests of laboratory staff in the hiring, promotion, and working conditions that impact their lives on a daily basis.

During her tenure at NIEHS, Sieber has received three Director’s Awards for her service to the Institute. She was also one of 16 members of the NIEHS family presented with the U.S. Department of Health and Human Services Secretary’s Award for Distinguished Service in 2006, as part of a group award for dedicated support of the health and safety of the Gulf Coast victims of Hurricanes Katrina and Rita.

Outside of work, Sieber has kept up her interests in recreation and enjoying the outdoors, including participation in NIEHS Health and Fitness Week competitions. She is an Amputee Coalition-certified peer visitor trainer and a Promoting Amputee Life Skills trainer at Johns Hopkins Center for Injury Research and Policy, as well as a support group leader of the Triangle Amputee Support Devils in Durham, N.C.



*Sieber clearly understands that attitude is an important part of living with a disability. Instead of considering the accident that changed her life to be a tragedy, she says she feels she has been given a second chance to live. Sieber also credits NIEHS workplace accommodation with helping her to continue as a productive employee. (Photo courtesy of Steve McCaw)*

Also named to SciMAC were new members Troy Turner, a military and prosthetics research representative, and David Dunville, a consumer representative. Turner is the research portfolio manager for Advanced Prosthetics and Neural Engineering at the Telemedicine and Advanced Technology Research Center for the U.S. Army Medical Research and Materiel Command. Dunville is an amputee support coordinator for H-Care Hurley/Binson's Medical Equipment, Inc. and president of the Amputee Firefighters Association.

## Coalition white paper addresses public health implications of limb loss

There is no question about the personal and financial burdens of limb loss on individuals, with healthcare costs for amputations alone, not counting prosthetics and rehabilitation therapy, reaching \$9 billion annually. These are issues that have long been at the forefront of advocacy and educational efforts by the Amputee Coalition.

According to a Coalition [report](#), each year, approximately 185,000 Americans undergo amputation of a limb and about 1,000 children are born with a limb difference. A 2005 estimate concluded that nearly 1.9 million people in this country are living with the loss of a limb.

Now, with a new white paper, "[Roadmap for Preventing Limb Loss in America](#)," released Sept. 11, an expert task force convened by the Coalition in February 2012 looks at the public health and health disparities issues involved with limb loss and its causes.

As the paper makes clear, there is much room for action to prevent limb loss. "There are nearly 2 million people living with limb loss in the United States," said Terrence Sheehan, M.D., medical director of Amputee Coalition and chief medical officer of the Adventist Rehabilitation Hospital of Maryland, in a Coalition [press release](#). "While not all limb loss is preventable, the leading causes of amputation — complications from diabetes and peripheral artery disease — can often be prevented through patient education, disease management, and regular foot screenings."

The white paper also takes aim at the disproportionate burden experienced by African-Americans, Hispanic and Latino Americans, and Native Americans, whose amputation rate is nearly four times that of white Americans. "It is essential that we reach out to these racial and ethnic groups that experience a higher incidence of diabetes and peripheral artery disease," Sheehan said. "Statistics show that 60 percent of the amputations resulting from diabetes-related complications could have been prevented and that roughly 85 percent of diabetes-related amputations are preceded by a foot ulcer."

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## "Silent Spring" turns 50

*By Eddy Ball*

Sept. 27 marked the 50th anniversary of the book credited with jump-starting the environmental movement, "Silent Spring," by marine biologist

Rachel Carson. It is a tribute to the power of this book, which has sold more than six million copies in 30 languages, that environmentalists valorize it and critics demonize it nearly as enthusiastically today as they did a half century ago.



Linked video:

[Watch a Voice of America video commemorating the 50th anniversary of the publication of Silent Spring \(02:59\)](#)

(Launches in new window)

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With its publication in 1962, “Silent Spring” made the public aware of the dangers of overuse of pesticides, just at the time when DDT was beginning to lose its efficacy, as insects grew more and more resistant to the chemical. Carson actually advocated a middle ground approach to insect control, to protect people from diseases such as malaria.

“No responsible person contends that insect-borne disease should be ignored,” she wrote in “Silent Spring.” “The question that has now urgently presented itself is whether it is either wise or responsible to attack the problem by methods that are rapidly making it worse.”

“The world has heard much of the triumphant war against disease through the control of insect vectors of infection, but it has heard little of the other side of the story — the defeats, the short-lived triumphs that now strongly support the alarming view that the insect enemy has been made actually stronger by our efforts,” Carson warned.

Carson’s argument had a nearly immediate impact at the highest levels of government, as President Kennedy issued the declaration that led to high-level study and vindication of Carson’s argument, leading to the ban of DDT in the U.S. in 1972.

Among the many leaders that Carson’s book influenced, including former Justice William Douglas and former Vice President Al Gore, who both wrote introductions for subsequent editions, was teenage scientist Linda Silber, who would assume leadership of NIEHS in 2009. NIEHS/NTP Director Linda Silber Birnbaum, Ph.D., has said that Carson’s powerful description of a silent spring, when overuse of pesticides has killed off birds, may well be one important reason her prediction hasn’t come true.



*In “Silent Spring,” Carson wrote, “As crude a weapon as the cave man’s club, the chemical barrage has been hurled against the fabric of life — a fabric on the one hand delicate and destructible, on the other miraculously tough and resilient, and capable of striking back in unexpected ways.” (Photo courtesy of the U.S. Fish and Wildlife Service)*



*In 1970, Carson’s previous employer, the U.S. Fish and Wildlife Service, presented a fitting posthumous tribute to the author of “Silent Spring,” when it dedicated the [Rachel Carson Natural Wildlife Refuge](#) in Maine. “Those who contemplate the beauty of the earth find reserves of strength that will endure as long as life lasts,” she wrote in her famous book. (Photo courtesy of the U.S. Fish and Wildlife Service)*

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# NIEHS celebrates Labor Day with public health presentation

By Eddy Ball

Most people wouldn't intuitively link workers' rights with public health, but for guest speaker Craig Slatin, Sc.D., they are inextricably connected. That was the message Slatin delivered to an audience at NIEHS Aug. 28 with his Labor Day presentation, "Labor and Public Health: Go Together Like a Horse and Carriage," hosted by NIEHS program analyst Bill Jirles, president of the American Federation of Government Employees (AFGE) Local 2923.

Sponsored by AFGE and the NIEHS Worker Education and Training Program (WETP), Slatin's talk placed contemporary labor and public health issues into historical context, as he built an argument for protecting workers and the environment, as both adjust to a changing economic landscape. "Transition strategies must try to solve economic and environmental public health issues simultaneously," he concluded, "or we can't solve either."

An associate professor and chair of the Department of Community Health and Sustainability at the University of Massachusetts (UMass) Lowell, [Slatin](#) is a veteran NIEHS grantee who is director of The New England Consortium (TNEC), the region's model Hazardous Waste Operations and Emergency Response (HAZWOPER) worker health and safety training organization. TNEC is based in the [Center for Health Promotion and Research](#) in the [School of Health and Environment](#) at UMass Lowell.

## Is social power a determinant of public health?

Slatin's review of labor and public health began with early efforts by reformers in England and Europe, who had to deal with the consequences of unregulated business and industrial activity during the spread of the Industrial Revolution, as production shifted from a small-scale, rural-based agricultural economy to the slums and factories of larger cities. Slatin explained that early students of the social and hygienic conditions of laboring people, such as France's Louis-Rene Villerme (1782-1863), protested child labor and the living conditions in the slums, but supported the hands-off principles of liberal economics.

However, with the beginning of the Chartist Movement in England in 1838, and the publication of "The Condition of the Working Class in England in 1844" by Friedrich Engels, political activists and social scientists began to see the economic system itself, rather than individual workers, as the real threat to environmental public health. "Engels called health disparities 'barbarism,'" Slatin explained, "and he saw social power as a determinant of health. To Engels, competition resulted in a social war — the war of each against all."



*According to Slatin, we must try to solve economic and environmental public health issues simultaneously. (Photo courtesy of Steve McCaw)*



*In his introduction, Jirles underscored the importance of Labor Day as a way of recognizing the contributions of American workers to the strength, prosperity, and well-being of the country. (Photo courtesy of Steve McCaw)*

## Fast forward to working conditions in post WWII America

With the decline in union membership, growing income disparity, and increasing globalization of the economy in the past 60 years, Slatin argued, America has entered a period of what he called neoliberalism that threatens workers' jobs and safety, as well as public health.

Among several examples, he pointed to the controversies surrounding the burning of coal for energy. As the use of coal declines in favor of clean sources, mine workers find their livelihood threatened, leading them to oppose the very clean air regulations that help protect their own health and the health of their families.

Although economic change is inevitable, Slatin concluded, a just transition strategy could help protect jobs when public health measures go into effect, or when offshore competition undermines such industries as textiles, automobiles, and furniture manufacturing. He pointed to worker training, tax reform, and green jobs as ways to achieve full employment and improve public health, as economies worldwide change at an unprecedented pace.

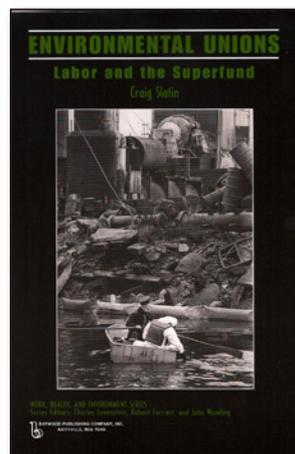
Slatin pointed to areas where the private and public sectors can collaborate to shape a workable strategy, by forming new and creative alliances with labor to advocate for reform and lay the foundations for a green jobs economy; developing new scientific models for environmental public health research and worker safety; and establishing the precautionary principle as a cornerstone of regulation of the growing number of untested chemicals in the environment.



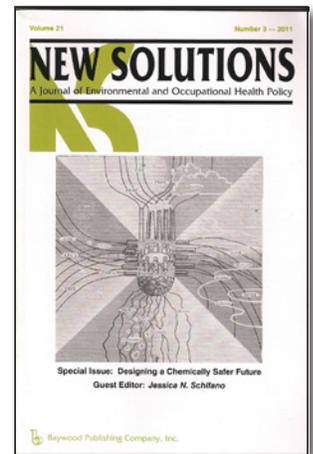
*The event attracted many NIEHS employees including Deputy Associate Director for Management Chris Long, whose team represents leadership in collective bargaining sessions with AFGE. (Photo courtesy of Steve McCaw)*



*WETP Director Chip Hughes, left, and program manager Sharon Beard, right, joined Slatin and Jirles following the talk. (Photo courtesy of Steve McCaw)*



*Slatin published his analysis of the role of labor in shaping the Superfund program in 2009. Among other topics, the book details the behind-the-scenes negotiations that resulted in the placement of WETP at NIEHS, rather than at the Center of Disease Control and Prevention National Institute for Occupational Safety and Health. (Image courtesy of Craig Slatin)*



*Slatin is also a member of the editorial board and the executive committee of New Solutions: A Journal of Environmental and Occupational Health Policy. New Solutions produces themed issues on emerging topics of interest to the labor and public health communities. (Image courtesy of Craig Slatin)*

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# Library staff in place and ready to assist

By Eddy Ball

Now that she has her full staff on board, contract Library Manager Erin Knight is eager to get the word out about how librarians can help advance science at NIEHS. With the hire of contract Technical Services Librarian Julie Harris in September, the NIEHS Library team now includes three full-time information professionals and one part-time staff member.

Harris joins Knight, contract Information Services Librarian Sandra Chambers, and Theresa Callahan, a contractor providing part-time administrative support to the Library.

## Taking the Institute's pulse about information services

With full staffing, Knight explained, the team now looks forward to continuing its ongoing support for Institute scientists, administrators, and other employees, as well as learning more about what people at NIEHS want and need from their library staff.

The library offers assistance with literature searches, citation and impact factor information, and quick reference help such as locating a new protocol. The information specialists are also available to assist on larger projects, and they encourage NIEHS staff to think beyond traditional librarian duties.



*Knight, seated, and the library team are poised to help patron service evolve to meet information challenges. Standing, left to right, are Callahan, Chambers, and Harris. "We're definitely going to be getting out and meeting as many people as we can to find out how we can help them," Knight said. (Photo courtesy of Steve McCaw)*

## Contact the NIEHS Library

Employees and visitors can access the library website internally through the Junction, e-mail staff, or call (919) 541-3426.

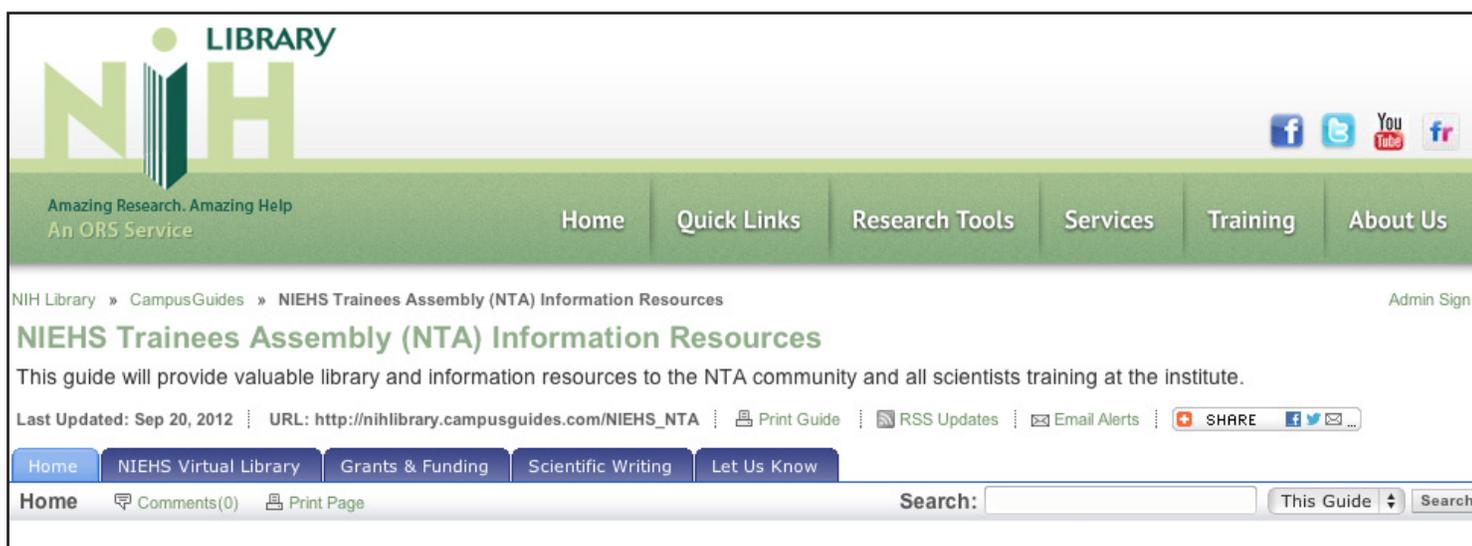
"We want to talk to people and find out how we can save people time and money, as well as help them get better quality information from professional databases, and even when appropriate, from Google," Knight said. "We're certainly encouraging new ideas for classes and other services."

Chambers emphasized that NIEHS employees need to understand how flexible the library staff can be. "We can also work one-on-one with people, if they can't make a class on the day scheduled or want training more tailored to their group's needs," she said. "They can just call us up and get one-on-one training or training for their department."

In addition, the team wants to take its services to an even higher level, especially in the areas of group and personalized training, Current Awareness search alerts for individual scientists,

outreach to new sectors of the NIEHS workforce, the management and expansion of special collections, and the kind of ad hoc individual information support the NIEHS Library has long prided itself in providing. In tandem with new levels and types of services, Knight wants to raise the library's profile by using many different communication vehicles and hosting events to increase awareness of the resources and services available to NIEHS.

As the needs of users change, the library team envisions pursuing more outreach initiatives. One example Knight cited is an emerging partnership with the Office of Fellows Career Development and the NIEHS Trainees' Assembly to develop workshops of interest to the trainees. Potential workshops on public and private funding for postdoctoral research and on how to search quickly across multiple databases are being discussed. In addition, Chambers just created a new library web guide for the trainees at the institute.



*In honor of Postdoc Appreciation Day Sept. 21, the library team created an [online library guide](#) customized especially for trainees at NIEHS.*

## Today's special library is more than books

The NIEHS Library still acquires new books each month and maintains an important reference section, but the real growth area of its collection is electronic — the more than 9,000 e-journals and 6,000 e-books that NIEHS researchers can access from their own computer terminals. The expansion of such electronic resources has been rapid, Knight noted, and the library staff can help scientists stay abreast of new developments that are relevant to research underway at NIEHS and acquire resources housed elsewhere through electronic and physical interlibrary loan.

The library is also responsible for overseeing special collections, such as the Rao Memorial Library of pathology resources, and the Work Family Life Collection. The library has many DVDs that employees can view onsite or check out for home or office viewing, including three new ones on Rachel Carson and “Silent Spring” in commemoration of the book's 50th anniversary, and the collection continues to grow.

The NIEHS Library is operated through a contract with CenterScope Technologies, Inc., which also provides library services for the U.S. Census Bureau and the National Institute of Standards and Technology.

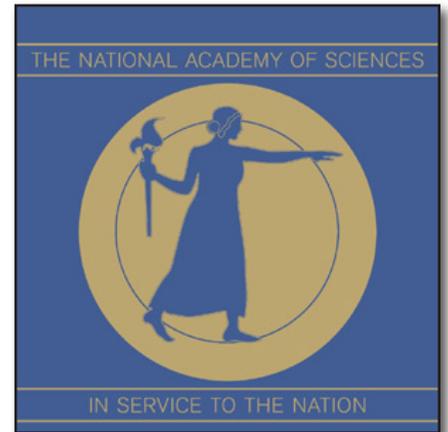
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# NRC report supports NIEHS vision of the exposome

*By Cindy Loose*

Advances in science and new technologies offer unprecedented opportunities for exploring the links between environment and disease, according to a new National Research Council report funded by NIEHS and the U.S. Environmental Protection Agency. The report, “[Exposure Science in the 21st Century: A Vision and A Strategy](#)” (ExpSci21), was released Sept. 7 by the National Academy of Sciences. The report can be purchased in hard cover online or downloaded in full or in summary as a PDF at no charge.

The report outlines several challenges in implementing systematic evaluation of the exposome, but it concludes that careful planning, advanced information management, and a spirit of partnership will help scientists realize that goal. “With focus, good science, and sustained support for research and development,” the report concludes, “exposure science will have a bright future.”



## The need and opportunity for exposure information

Traditionally, scientists studying the impact of environment on disease have focused on one exposure at a time. The ExpSci21 report envisions the use of ubiquitous sensing networks to collect personal exposure information on multiple pollutants across scales from individuals to ecosystems and across multiple dimensions of time, in an effort to characterize the totality of exposures throughout the life course, a concept that has been dubbed the exposome.

New technologies can greatly enhance efforts to focus on a systematic evaluation of the totality of exposures over a lifetime, the report emphasized. Emerging tools for exposure assessment, such as those developed by the NIEHS Exposure Biology Program, integrating high-tech sensor technologies, global positioning systems, genomic techniques, and informatics are critical needs for achieving this goal.

The greatest challenge of the past has been too little data on exposures. The challenge of the future will be a massive data wave that will require new ways of analyzing information, said Kirk Smith, Ph.D., chair of the committee of 19 academic researchers who prepared the report. Smith is a professor of global environmental health at the University of California, Berkley. According to the authors, a critical piece of the ExpSci21 vision is the need for a publicly available data infrastructure for sharing and analyzing multi-component exposure information.

Exposure science is playing a fundamental role in many fields of environmental health, but can also be applied to environmental regulation, urban and ecosystem planning and disaster management, the report noted. It envisioned adoption of the concept of an eco-exposome, in which exposure science extends from the point of contact between stressor and receptor, inward to an organism, and outward to the environment.

## Realizing the vision

In the near term, exposure science needs to develop strategies to rapidly improve understanding of when, where, and how exposures occur, in addition to their health significance. The report calls for the development of a new exposure infrastructure, such as sensor networks, to help identify knowledge gaps and allow scientists to identify and prioritize the most urgent targets for research, based on both the burden of exposure and the potential for toxicity.

The report urges enhanced multi-agency collaboration. It notes that the report “Toxicity Testing in the 21st Century: A Vision and A Strategy” spurred the development of Tox21, which has made great advances by pooling the resources of NIEHS, NIH, EPA, the Food and Drug Administration, and the National Toxicology Program. That model, the report said, could be extended to exposure science and the creation of Exposure21. Such a collaboration, it added, would need to be extended to other federal agencies such as the Centers for Disease Prevention and Control, U.S. Geological Survey, and National Aeronautics and Space Administration.

(Cindy Loose is a contract writer with the NIEHS office in Bethesda, Md.)

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# Science Notebook

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## Birnbaum talks science and strategy at Dioxin 2012

*By Eddy Ball*

NIEHS/NTP Director Linda Birnbaum, Ph.D., was one of nearly a thousand delegates attending Dioxin 2012, where she made three invited oral presentations and was lead researcher on four poster presentations.

The meeting, held Aug. 26-31 in Cairns, Queensland, Australia, attracted scientists from throughout the world to the [32nd International Symposium on Halogenated Persistent Organic Pollutants — Dioxin 2012](#), offering Birnbaum an international forum for raising awareness of NIEHS advances in the promotion of environmental public health.

The program covered a broad range of core topics on analytical and environmental chemistry, environmental and human toxicology, epidemiology, and exposure assessment, as well as regulation, risk assessment, and management. Focal points for the meeting were emerging contaminants, marine and ecotoxicology, and chemical regulation and policy.

### **Engaging the unique toxicology of endocrine disrupting chemicals**

Birnbaum addressed an emerging paradigm for understanding the health effects of endocrine-active chemicals, such as the flame retardant chemicals she studies in her lab at NIEHS, in her first talk Aug. 27, “Endocrine disruptors: Where do we go from here?”

The presentation surveyed the increasing rates of diseases with a probable link to the environment and the many chemicals that scientists have shown to have effects on the endocrine system, triggering adverse effects on reproductive function, brain development, lung function, and other physiological properties that rely on proper development and optimal endocrine function in order to maintain health. Then, she introduced the concept of nonmonotonic dose response, the pattern seen in exposure to hormones and endocrine-active chemicals found virtually everywhere in the environment.

“Modern science around toxicology has moved beyond the simple dichotomy of toxic versus nontoxic, which implies that all substances can be harmful at high doses, and at some lower dose, no harm is done,” she explained. “A nonmonotonic relationship [in contrast] allows for decreases in the effect at some doses and increases at others.”



*One of Birnbaum's important messages is that primary prevention is the best, and often the most cost-effective, way to promote public health.  
(Photo courtesy of the University of Illinois)*

These effects can be long lasting, Birnbaum explained in the course of the talk. “Exposure to endocrine disruptors during development can result in profound changes in later life ... by subtly altering the structure of the DNA molecules and chromosomes,” she said. “These changes can potentially affect gene expression for several generations. This is the relatively new science of epigenetics.”

### **The strategic plan — integrating toxicology and risk assessment**

The next day, Birnbaum turned to the new NIEHS strategic plan with her talk on “Environmental health research at NIEHS: current priorities and plans for the future.” The presentation described the year-long process of creating the plan’s mission statement, addressed its vision, and discussed each of the 11 strategic goals.

Following her discussion of implementing the strategic plan, with its overall commitment to translating bench science into environmental public health, Birnbaum underscored the public health implications of environmental effects and the impressive return on investment that can be achieved through environmental interventions.

Pointing to a New England Journal of Medicine [study](#) published this summer, she told the audience, “Environmental interventions are generally more cost-effective than clinical interventions, such as medical care and vaccines, and such non-clinical person-directed interventions as personal exercise programs. ... This [study] suggests that there may be many cost-effective environmental interventions that are not yet recognized and deserve more attention.”

### **Wrapping up — a personal perspective**

Birnbaum was also one of six distinguished speakers featured in the “Plenary Series: State-of-the-Art and Future Challenges” session Aug. 31 that brought Dioxin 2012 to a close. Her talk surveyed the area of toxicology and health, with a presentation titled “Key recent achievements in toxicology and health: a personal perspective.”

The talk could easily have been subtitled “Lessons learned in the course of a three-decades career in toxicology,” as Birnbaum ranged across a number of areas where experience has caused her to question conventional wisdom and pat assumptions. Topics included health effects of concern, critical windows of sensitivity and susceptibility, effects of exposure to mixtures and low dose effects, and the role of lipid adjustment in moderating toxicity.

“We haven’t learned our lessons,” Birnbaum said, before she ended the presentation with a question that also served as a challenge. “Why are we still allowing persistent, bioaccumulative chemicals to enter the marketplace?”

*Citations:* Blum A, Babrauskas V, Birnbaum L. Replacements for pentaBDE flame retardant: Is there an improvement in fire safety or health impacts?

Schechter A, Lorber M, Guo Y, Wu Q, Yun SH, Kannan K, Miller J, Hommel M, Imran N, Hynan LS, Cheng D, Colacino J, Birnbaum LS. Phthalates and hexabromocyclododecane (HBDE) in U.S. Food.

Sanders JM, Knudsen GA, Birnbaum L. The disposition of beta-hexabromocyclododecane (HBCD) in mice.

Scott L, Mortimer D, Birnbaum L. Brominated flame retardants (BFRs) in food and food products and impact of dietary intake on body burden: policy implications for regulating BFRs in the U.S.

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# Models take spotlight at council science talks

By Ernie Hood

Advances in animal models were the focus of two scientific presentations at the Sept. 11 National Advisory Environmental Health Sciences Council meeting. Zebrafish and mice have been model organisms in environmental health sciences for a long time, but today researchers are crafting bold innovations to advance their usefulness as vehicles for scientific inquiry into toxicity and disease.

Council members were treated to exciting, informative talks by NIEHS Superfund Research Program grantee [Robert Tanguay, Ph.D.](#), a distinguished professor of molecular toxicology and head of the Sinnhuber Aquatic Research Laboratory at Oregon State University; and lead researcher [Jef French, Ph.D.](#), head of the NTP Host Susceptibility Group within the Biomolecular Screening Branch.

## Harnessing the power of zebrafish

In Tanguay's lab, the goal is to link phenotype with genotype, using zebrafish, which closely resemble humans in terms of responses to environmental insults and disease traits. Several years ago, Tanguay realized there were major bottlenecks in the process. He and his team used funding from the American Recovery and Reinvestment Act of 2009, to focus intensive efforts on streamlining and accelerating the lab's ability to produce the fish and run them efficiently through toxic exposure assays.

"We needed to crank it up," he told the Council audience. "We identified that if we were going to take full advantage of this model, we needed to massively increase the robustness of phenotype discovery, to link exposure to phenotype, to identify a mechanism."

Crank it up they did, achieving a quantum leap in experimental productivity by engineering several ingenious new processes to break the bottlenecks, including highly automated methods to allow unlimited production of zebrafish embryos, nondestructive handling of the embryos, and chorion removal, where the embryo's outer membrane is excised to permit direct exposure of the developing embryo to challenge toxicants. Those innovations allowed the use of high-throughput technology to run experiments designed to gauge the impact of exposures, including mixtures, on the very early development of the zebrafish, with measurable endpoints in just five days.



*Tanguay and his group, whose motto is "Thinking outside the tank," have pioneered new methods allowing zebrafish assays to be run in high-throughput equipment. "We realized that there were a lot of ways to impact the environmental health sciences field, if we could automate several of the steps in the process," he told Council. (Photo courtesy of Steve McCaw)*



*Thanks to innovations by Tanguay's lab and others, the humble zebrafish has achieved supermodel status in the scientific world. (Photo courtesy of Robert Tanguay)*

Today, thanks to his group's technological advances, the zebrafish is poised to take on supermodel status. "We can translate the data in many different ways, such as identifying inherently hazardous compounds," said Tanguay. The approach also supports a process he calls binning. "Once you have the ability to massively do exposures with lots of different compounds, with known structures or known mixture composition, you then have the ability to associate the chemical structure and the composition with the biological responses you get, and start binning the compounds based on the commonalities of responses and structure. And, then, you can drill down from representative members of these families to define the actual cause of toxicity."

### Mouse models have it both ways

French shared the results of recent experiments with two types of mouse models — a fixed-genotype, inbred, 18-strain panel known as the NTP panel, and a highly genetically diverse mouse population called the Diversity Outbred (J:DO) mouse, where random outbreeding was used to scramble the genomes of eight laboratory and wild-derived mouse inbred strains into a new wild-type mouse population, where every mouse is genetically different from every other mouse.

He described assays exposing both models to benzene, a ubiquitous toxicant in the environment with a large amount of existing data on the effect on metabolism, toxicity, and carcinogenicity, which are remarkably similar between humans and rodents.

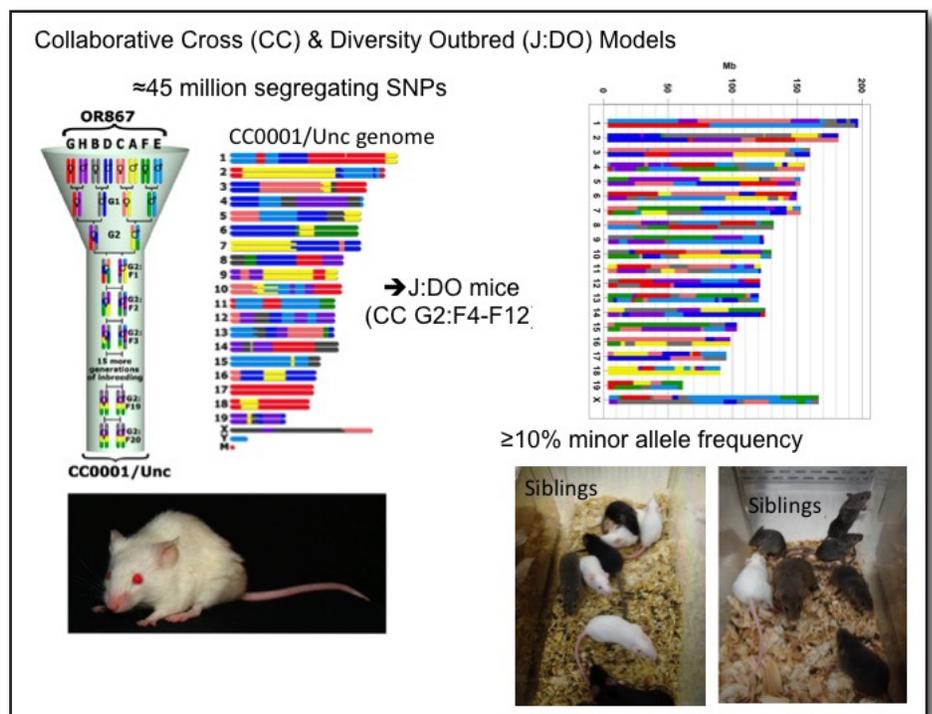
A haplotype association mapping approach was used with the inbred strains to allow characterization of their benzene absorption, distribution, metabolism, and excretion phenotypes.

Experiments with the J:DO mice were designed to assess benzene-induced hematotoxicity and genotoxicity, following 28 days of controlled inhalation exposures at low levels.

According to French, both approaches — measuring inter-individual variability and population-level variability — are valuable in the effort to link genome-by-environment interactions with human outcomes. They will also help to quantify the uncertainty factors in correlations between mouse and human.



French said he appreciated the opportunity to update Council on advances in experimental mouse models. French has built upon insights from the NIEHS *Mouse Genome Resequencing and SNP Discovery Project*, in the search for a mouse model with genetic diversity more similar to that found in humans. (Photo courtesy of Steve McCaw)



Representative genomic structure maps, and photos of an inbred Collaborative Cross mouse, left, and outbred J:DO siblings, underscore the extent of diversity found in the outbred population. (Photo courtesy of Jef French)

“Based on the studies performed using the J:DO mouse population, we conclude that population-based models are warranted in *in vivo* toxicology, in order to determine the role of inter-individual variability, and identify resistance and susceptibility alleles associated with population-based outcomes,” French said. “I emphasize that we have identified a number of candidate genes that may be major determinants of these phenotypes, but after this discovery phase, using the forward genetics approach, we must return to reverse genetics and molecular biology, to validate their function and the mechanistic basis for the observed toxicity.”

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

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## Mouse studies may help unravel human illnesses

By Robin Arnette

Can studying mice help scientists better understand human diseases? According to this month’s NIEHS Distinguished Lecturer, mouse geneticist Monica Justice, Ph.D., the answer is a resounding yes.

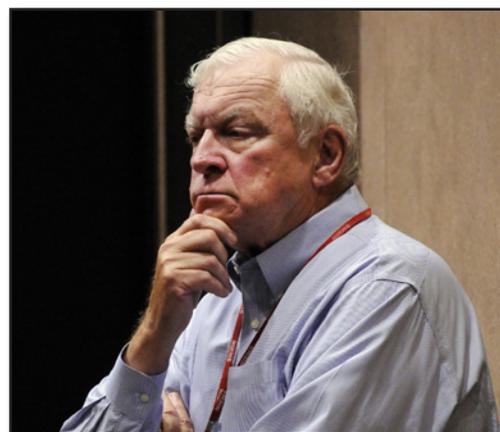
[Justice](#) is a professor in the Department of Molecular and Human Genetics and director of the Mouse Embryonic Stem (ES) Cell Core Facility at Baylor College of Medicine in Houston, Texas. She came to NIEHS Sep. 13 to talk about the second phase of the Knockout Mouse Project (KOMP) called KOMP2. KOMP2 is funded by the National Institutes of Health and is an initiative for three centers at Baylor College of Medicine, the University of California-Davis, and The Jackson Laboratory. The project focuses on the phenotypic analysis of mice, or the study of the physical makeup of mice as determined by genetic and environmental influences. She hopes the new program will reveal the function of genes in the mammalian genome.

Justice contributes to KOMP2 by heading the [BaSH consortium](#), a collaboration of Baylor College of Medicine, the [Sanger Institute](#), and the [MRC Harwell Mouse Genome Centre](#), United Kingdom. She said the idea for KOMP2 originally came from a 2003 gathering of mouse geneticists at Cold Spring Harbor who wanted to knockout all of the genes in the mouse genome to better understand human sequencing studies. The work has now grown to become part of a larger international effort called the International Mouse Phenotyping Consortium (IMPC), with KOMP2 serving as one of the founding members.

“We are developing standard phenotyping platforms, as well as common quality control standards for the program,” Justice said of KOMP2’s contribution to IMPC. “Our goal is to produce a global resource of knockout mice and an entire database of gene function for all of the genes in this program.”



*Justice said that 70 percent of lethal homozygous mutations produce related phenotypes in adults as heterozygotes. She said, “We think these are the ones that are more likely to model human diseases since many human diseases are really semi-dominant in origin, and not recessive.”*  
(Photo courtesy of Steve McCaw)



*As head of the NIEHS Mouse Information Management System, Schrader said phenotyping data would greatly improve the current system.*  
(Photo courtesy of Steve McCaw)

## KOMP2 finds previously unknown gene functions

According to Justice, KOMP2 has 14,000 conditional-ready ES cells, or ES cells for 14,000 genes, which will be transmitted into mice that will undergo phenotyping. The phenotyping pipeline tests neurological behavior, metabolism, cardiovascular, pulmonary, reproduction, sensory, muscular-skeletal, immune, and general overall health.

One of the first genes KOMP2 examined is called *Akt1s1*. Justice said that it links energy and nutrients to cell growth and metabolism and is known to function in human cancer and type 2 diabetes. After knocking out *Akt1s1*, they noticed that the homozygotes died prior to embryonic day 12.5 with complete cardiovascular failure, suggesting that the gene's primary function may involve the circulatory system.

The researchers then took the heterozygotes through the phenotyping pipeline, and tests revealed these mice had abnormal glucose clearance, regressed vasculature in the eye, and an increased pause and breath frequency as compared to wild-type mice. Justice said that the KOMP2 phenotyping pipeline is invaluable in characterizing genes because the results identify excellent human disease models to study.

NIEHS Deputy Scientific Director William Schrader, Ph.D., invited Justice and served as host for the seminar because the Institute is interested in carrying out its own neurobiological testing of mice. He knew that NIEHS would benefit from her expertise.

“Dr. Justice not only provided NIEHS with an excellent scientific seminar, but she also shared her considerable experience in mouse phenotyping with [Scientific Director] Dr. Zeldin and the Division of Intramural Research investigators who require this capability,” Schrader said.

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## Allergy research uncovers heart attack link

*By Robin Arnette*

People with allergies are less likely to have experienced a heart attack, according to a new study by scientists at NIEHS and SRA International. The research appeared [online](#) Aug. 23 in the *Journal of Allergy and Clinical Immunology* and is the first to measure the presence of allergic antibodies in relation to past myocardial infarction (MI) in the U.S.

The work was based on laboratory data and questionnaires from the [National Health and Nutrition Examination Survey \(NHANES\) 2005-2006](#), a cross-sectional analysis of the U.S. population developed in collaboration with NIEHS, the National Institute of Allergy and Infectious Diseases, and the National Center for Health Statistics. Using thousands of participants, the research team measured allergic antibodies, also known as allergen-specific immunoglobulin E (sIgE), that were specific to 19 allergens, and then examined the relationship between sIgE and self-reported past heart attack.



*Christopher Campos, Ph.D., is an Intramural Research Training Award (IRTA) fellow in the Laboratory of Toxicology and Pharmacology. He studies how therapeutic agents cross the blood-brain barrier in rodents and was interested in several of the phenotyping tests Justice discussed. (Photo courtesy of Steve McCaw)*

“We looked at it in a few different ways quantitatively, and any way we looked at it, we found an inverse relationship with past heart attack,” said corresponding author and NIEHS lead researcher [Michael Fessler, M.D.](#) “The findings are a preliminary step forward, but if our results are confirmed in a prospective study, this could lead to important clinical implications for how allergen exposure affects people’s risk for heart attack.”

### **Immune programming**

Fessler said that the paper was based on studies of the adaptive immune system, or the body’s ability to develop memory for environmental molecules. He said adaptive immunity is largely driven by different immune programs that involve T helper (Th) cells.

Previous work from other laboratories determined that mice born with a Th1 immune program tend to develop atherosclerosis and other inflammatory diseases, while those with Th2 generally develop allergies and are protected from atherosclerosis. His group wanted to see if people who are allergic to food, grasses, pet dander, and other substances were less likely to have had a heart attack, based on the premise that Th2 allergic programming, as indicated by sIgE, might suppress the Th1 immune response required for atherosclerosis.

Since NHANES is a cross-sectional analysis of people in the country, Fessler and colleagues can’t definitively say that having allergies will protect someone from having a heart attack. Nonetheless, NIEHS Scientific Director and article co-author Darryl Zeldin, M.D., believes the findings are significant.

“The data are still intriguing, given that the relationship is independent of a long list of coronary risk factors, such as smoking, high cholesterol levels, hypertension, family history of MI, and diabetes,” Zeldin said.

*Citation:* [Jaramillo R, Cohn RD, Crockett PW, Gowdy KM, Zeldin DC, Fessler MB.](#) 2012. Relation between objective measures of atopy and myocardial infarction in the United States. *J Allergy Clin Immunol*; doi:10.1016/j.jaci.2012.06.033 [Online 23 August 2012].

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*Fessler said the work allows researchers to examine the connection between allergies and heart attack in more detail. “For instance,” Fessler proposed, “if you started with an atherosclerotic mouse model, and made it allergic to a particular allergen, would you reduce atherosclerosis in that animal?” (Photo courtesy of Steve McCaw)*



*Zeldin is an expert on indoor allergies and is involved in several studies that test the effectiveness of strategies that reduce allergen levels in inner-city homes. (Photo courtesy of Steve McCaw)*

# New strategy may improve delivery of medicines to the brain

By Robin Arnette

NIEHS researchers offer a possible strategy for treating central nervous system diseases, such as brain and spinal cord injury, brain cancer, epilepsy, and neurological complications of HIV. The experimental treatment method allows small therapeutic agents to safely cross the blood-brain barrier in laboratory rats by turning off P-glycoprotein, one of the main gatekeepers preventing medicinal drugs from reaching their intended targets in the brain. The [findings](#) appeared online Sept. 4 in the Proceedings of the National Academy of Sciences.

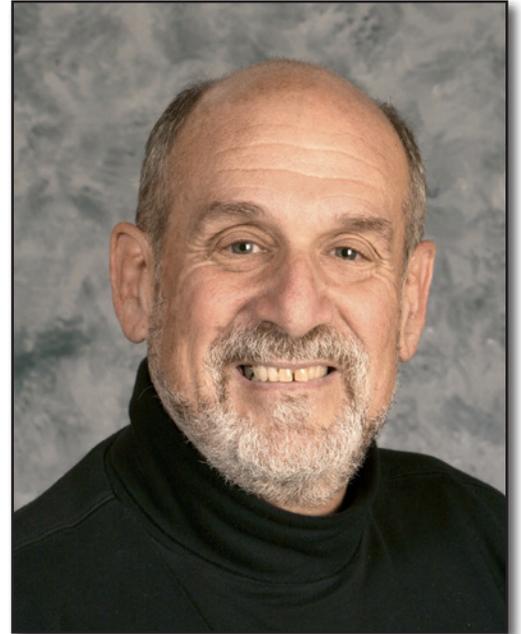
“Many promising drugs fail because they cannot cross the blood-brain barrier sufficiently to provide a therapeutic dose to the brain,” said [David Miller, Ph.D.](#), head of the Laboratory of Toxicology and Pharmacology at NIEHS, and leader of the team that performed the study. “We hope our new strategy will have a positive impact on people with brain disorders in the future.”

In a two-pronged approach, the research team first determined that treating rat brain capillaries with the multiple sclerosis drug marketed as Gilenya (fingolimod) stimulated a specific biochemical signaling pathway in the blood-brain barrier that rapidly and reversibly turned off P-glycoprotein. Team members then pretreated rats with fingolimod and administered three other drugs that P-glycoprotein usually transports away from the brain. They observed a dramatic decline in P-glycoprotein transport activity, which led to a threefold to fivefold increase in brain uptake for each of the three drugs.

[Ronald Cannon, Ph.D.](#), staff scientist in the Miller lab and first author on the paper, said one of the burning questions the team wants to tackle next is to understand how the signaling system turns off P-glycoprotein. He equates the mechanism to what happens when a person flips a light switch.

“If you physically turn off a light using the button on the wall, the light will go out because the electrical current to the light bulb has been interrupted,” Cannon explained. “But what happens when the signaling pathway shuts down P-glycoprotein? Does it bring in another protein to bind to the pump, take away its energy source, modify the structure of the pump, or something else?”

Cannon said the paper’s findings open a new way of thinking about targets for drug design, a prospect that is emotionally gratifying for him and many other researchers whose scientific discoveries generally don’t directly translate into helping people with illnesses.



*Miller has studied P-glycoprotein for 15 years and considers it a major determinant of the therapeutic drug uptake in the body, distribution among tissues, and excretion out of the body. It is especially important in the blood-brain barrier, where it limits movement of drugs from the blood to the brain. (Photo courtesy of Steve McCaw)*



*Cannon said, “I’m very excited to be part of this work because these findings have real clinical relevance.” (Photo courtesy of Steve McCaw)*

“Although much more research needs to be done, delivering therapeutics to the central nervous system is one of the final frontiers of pharmacotherapy,” Cannon added.

*Citation:* Cannon RE, Peart JC, Hawkins BT, Campos CR, Miller DS. 2012. Targeting blood-brain barrier sphingolipid signaling reduces basal P-glycoprotein activity and improves drug delivery to the brain. Proc Natl Acad Sci U S A; doi:10.1073/pnas.1203534109 [Online 4 September 2012].

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## Epigenetic studies can shed light on causes underlying complex disease

By Ashley Godfrey

In a seminar Sept. 10 at NIEHS, grantee Robert Wright, M.D., explained the importance of epigenetics in reproductive health research. Wright, who is director of the division of environmental health at Mount Sinai School of Medicine, spoke to a capacity audience gathered to hear his presentation, “Environmental Epigenetics and Reproductive Health.”

As Wright explained, epigenetic changes, often called marks, regulate gene expression without changing DNA sequence. Epigenetics is a separate cell code allowing cells containing the identical DNA sequence to differentiate into distinct cell types, such as neurons or epithelial cells.

These marks regulate if and when specific genes are expressed, and drive many of the interactions between genes and environment. Epigenetic marks are modifiable and can be important mediators for the effects of environmental exposures, such as toxic chemicals. Environmental modification of epigenetic marks in specific tissues may be the mechanism behind complex diseases, such as fetal growth restriction.

### Understanding the importance of DNA methylation

“Epigenetic studies, like those underway by Dr. Wright and his colleagues, will help us understand the mechanisms underlying exposure-disease associations,” stated Todd Jusko, Ph.D., a fellow in the NIEHS [Biomarker-based Epidemiology Group](#) and host for Wright’s visit.

DNA methylation is the most studied epigenetic mark. Wright is interested in studying methylation patterns in DNA taken from target tissues critical to fetal growth, such as umbilical cord blood vessels and placenta. A toxic chemical that reduces growth would likely alter methylation in one or all of these tissues. Wright and his colleagues believe this approach will shed light on some of the factors that influence fetal growth restriction.



*After his seminar, Wright gave a separate talk to NIEHS fellows and other trainees from around the area. Wright shared his experience of many years of writing and receiving grants, and offered his advice to the young scientists about how to both be successful and deal with rejection. (Photo courtesy of Steve McCaw)*

## Why is reproductive health so well suited to epigenetic research?

Epigenetics differs from genetics in that the cell type that is being studied is a critical component of the research, whereas DNA sequence is the same in all cells. Genomic DNA methylation patterns vary by cell type. For this reason, studying methylation from DNA collected from white blood cells may not be relevant to neurodevelopmental health. Brain tissue is needed for such a study, which has obvious drawbacks.

In contrast, the tissues important for studying fetal growth are easy to access noninvasively and typically are discarded after delivery. In this research, Wright has partnered with [Andrea Baccarelli, M.D., Ph.D.](#), of the Harvard School of Public Health, to scan the methylome of multiple target tissues relevant to fetal growth — placenta, umbilical artery, umbilical vein, and cord blood. Using a comprehensive analysis of DNA methylation throughout the genome, they will extend this pilot study to a larger set of children.

Wright hopes the results will help answer the question of whether methylation patterns mediate common environmental risk factors for fetal growth restriction, and ultimately point to potential therapeutic and preventive strategies. “The promise of epigenetics is [that] the marks are modifiable, unlike DNA sequence,” he said.

## Looking for function in a desert of non-function

One of the questions Wright wants to study is whether methylation of noncoding DNA is important to health. Wright is interested in studying DNA methylation in genomic areas traditionally believed to be non-functional, so-called repetitive elements. Once called junk DNA, these areas account for more than 50 percent of the total DNA sequence.

Repetitive elements are large pieces of ancient DNA sequence that originated from viruses and contain the same sequence repeated throughout the genome. According to Wright, one third of the total DNA methylation occurs within these elements.

According to new research published by the [Encyclopedia of DNA Elements \(ENCODE\) consortium](#), there is evidence that repetitive elements may have evolutionary function. It is known that repetitive elements can move and reinsert in new places in the genome. At the individual level, this transposition might lead to overt disease, such as cancer, or cause subtle effects on gene expression.

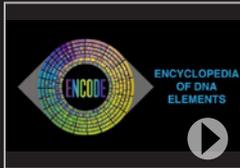
Wright is interested in finding out whether repetitive element transposition can be affected by environmental or other factors in chronic disease development. “We [as researchers] have consistently underestimated the importance of these elements,” he concluded.

*Citation:* [Wright RO, Schwartz J, Wright RJ, Bollati V, Tarantini L, Park SK, Hu H, Sparrow D, Vokonas P, Baccarelli A.](#) 2010. Biomarkers of lead exposure and DNA methylation within retrotransposons. *Environ Health Perspect* 118(6):790-795.

(Ashley Godfrey, Ph.D., is a postdoctoral fellow in the Molecular and Genetic Epidemiology Group in the NIEHS Laboratory of Molecular Carcinogenesis.)



*“Dr. Wright’s visit to NIEHS was a tremendous opportunity for trainees in the Epidemiology Branch to learn about the grant writing process from a senior extramural investigator within our discipline,” stated Jusko. “We also opened up the grant writing seminar to trainees in epidemiology at local universities and received a great turnout.”*  
(Photo courtesy of Steve McCaw)



**Linked video:**  
[Watch a Nature Video presentation on the ENCODE project \(04:27\)](#)

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# Challenges persist in the critical task of determining safety of nanomaterials

By Cindy Loose

Experts from industry, academia, unions, and government explored questions about occupational safety of nanomaterials, at a two-day [workshop](#) Sept. 10-11 in Washington, D.C.

“The diversity and variety of engineered nanomaterials is tremendous, so the problem is particularly complex,” said NIEHS Senior Advisor Christopher Weis, Ph.D., during his presentation on concerns about how nanomaterials may affect living cells and organs.

## Nanomaterials: promise and concerns

Already, thousands of products — clothing, food, sporting goods, and medicines, to name a few — are manufactured using engineered nanomaterials (ENMs). ENMs are extremely small, with at least one dimension no larger than approximately 1 to 100 nanometers. One nanometer is about 100,000 times smaller than the diameter of a human hair.

The promise of nanotechnology is great. Nanomaterials can, for example, make cement, cloth, and other materials stronger and more durable, yet lighter. Nanotechnology is also invaluable in electronics and drug delivery.

However, by definition, nano-sized particles have unique properties. Thus, even well-studied materials considered safe, such as silver, may pose a hazard when engineered to nano size. Nano-sized particles can enter the human body through ingestion, inhalation, and absorption through the skin, and certain nanoparticles have produced toxicologic reactions in the lungs of exposed experimental animals, according to published studies [reviewed](#) by the Occupational Safety and Health Administration.

In his workshop presentation, “Strategies for Setting Occupational Exposure Limits for Engineered Nano Materials,” Weis said, “Human exposure to ENMs is not theoretical — it is occurring everyday.” He noted that the respiratory system offers a large surface area for damage to occur. At the same time, he added,

## Persistent questions remain about the safety of nanomaterials

How can experts determine safe exposure levels for workers who handle nanomaterials whose properties remain a mystery?

How can exposure levels even be measured?

Who should be involved in determining safety?

Which nanoparticles might pose the most hazard and thus should get priority in toxicity studies?

These are just some of the questions being studied through cross-divisional efforts funded by NIEHS.



NIEHS representatives enjoy the fresh air during a workshop break. Shown, left to right, are Weis, Saunders, and Popovech. “[Nanotoxicology is] uncharted territory but, with preliminary data, we are definitely seeing changes in gene expression in key oxidative stress genes in both the lungs and livers of animals exposed to silver nano particles,” Popovech said. (Photo by Cindy Loose)

the bronchial alveolar area of the lung, which allows exchange of oxygen and carbon dioxide, is a delicate membrane only 0.2 microns thick. Damage to this membrane can cause an inflammatory response, as well as lung disease.

“Keeping particles out of this space is the goal,” he said. He added that nanoparticle behavior is dictated by their surface area and chemistry. When seeking safe levels of exposure to a particular nanoparticle, it is essential to consider particle shape, surface area, and physical chemistry of the corona of molecules on the particle’s outer layer. Weis noted that NIEHS is researching what populations may be more susceptible than most to potential nano hazards.

### **Additional perspectives**

NIEHS grantee [Günter Oberdorster, D.V.M., Ph.D.](#), who presented on a panel with Weis, discussed the intricacies of hazard identification, exposure assessment, and risk management. As did many present, he lamented the lack of data currently available, but added, “Efforts at the workshop are very important, as we at least begin making decisions about how to establish occupational exposure levels.”

Two young Ph.D. candidates who are working on an NIEHS-sponsored project headed by [Terry Gordon, Ph.D.](#), at New York University (NYU), discussed their excitement and sense of purpose from working on nanotechnology from the perspective of environmental health.

“It is such a novel field,” said Mary Popovech. “The things we’re doing, no one has ever done before.” She is researching the effect on mice of inhaled exposures to silver nanoparticles, and the effect on their genes, which has implications for future generations.

Her NYU colleague, Eric Saunders, said his intention was to get a job after finishing his master’s degree, but his work on the NIEHS-funded project convinced him to stay for a Ph.D. and see the project through to the end. “The work,” he said, “is too important to abandon.”

The workshop, held at George Washington University, was sponsored by the American Chemical Council’s Nanotechnology Panel and the university. It drew more than 100 participants, most committed to being involved in continued efforts to develop a strategy to ensure workplace safety in this new and emerging technology.

(Cindy Loose is a contract writer with the NIEHS office in Bethesda, Md.)

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## **Integrating learning and memory tests into developmental neurotox studies**

*By Sheetal Thakur*

An enthusiastic audience of toxicologists and neuroscientists was on hand Sept. 6 to hear a presentation by animal behavioral testing expert Charles Vorhees, Ph.D.

Vorhees’ seminar, “Assessment of Learning and Memory in Developmental Neurotoxicology Studies,” was hosted by his longtime research associate, NTP neuroscientist [Jean Harry, Ph.D.](#), who had invited him to share insights from his extensive experience in using rodent models for evaluating effects of neonatal exposures to toxicants that later in life lead to behavioral and cognitive impairment.

The seminar was organized as a part of NTP's efforts to collaborate with basic researchers, in the course of developing and validating improved testing strategies and strengthening scientific knowledge on potential developmental toxicants.

**Vorhees** is a professor of pediatric neurology and director of the Animal Behavioral Core in the Cincinnati Children's Hospital Medical Center at the University of Cincinnati (UC). He is a leading authority in the field of behavioral toxicology and has published numerous articles on chemical-induced and drug-induced alteration of learning and memory in laboratory animals.

### **Advantages of mazes for testing learning and memory**

Vorhees began his talk by highlighting the distinction between learning and memory. He added that both learning and memory can be classified into different types and pointed to subtle differences between different types of memory. He emphasized that it is crucial for researchers to know what kind of memory they are testing and to select a testing paradigm that addresses the specific scientific question. Different types of memory are stored in different parts of the brain and memory circuits involved can change dramatically between types.

Learning and memory tests can be broadly classified into the operant-type and mazes, and according to the type of reinforcement used. In the context of regulatory toxicology studies, Vorhees recommended maze testing, with escape from water serving as the motivator, but offered caveats about the inherent limitations of any single model of testing.

“Swimming mazes are basically immune to appetite differences,” said Vorhees. This could be a major advantage for testing toxicants that affect appetite and growth. From the screening perspective, these mazes require little or no training, are unaffected by body mass differences, and the motivation is intrinsic. In addition, they have adequate learning curves, no dropouts, and moderate inter-individual differences, and can be integrated and expanded to more complicated types of assessment. He cautioned on the use of certain types of tests, such as passive avoidance tests and simple T, Y, and M mazes, which have certain confounding factors associated with them, including aversive motivation and strain differences in response.

### **Things to consider while choosing the right test**

Vorhees stressed that learning and memory involve a complex set of functions, and there is no single test that can address all aspects of learning and memory. He emphasized the importance of a standardized and validated testing approach. “It worries me that in contract laboratory settings the emphasis is on efficiency rather than validity,” he added.

Vorhees encouraged researchers to use a robust negative control, and choose tests that have low false positives and negatives. He explained that before starting a testing paradigm, it is important to understand the pros and cons of each test, and to consult external experts when necessary.



*Vorhees stressed that researchers should be clear about their objectives when they design their studies. They need to understand what aspect of learning and memory is being studied, and whether the study is for screening or in-depth analysis, as well as the pros and cons of the tests being considered. (Photo courtesy of Charles Vorhees)*

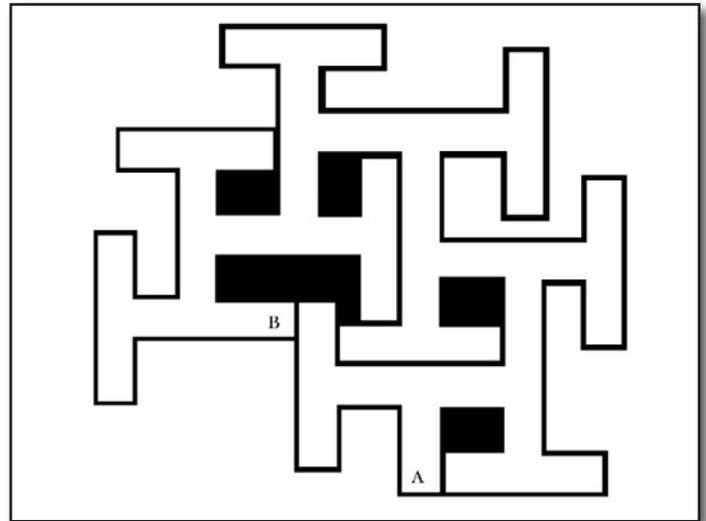
According to Vorhees, some of the commonly used tests in laboratory settings include the Morris Water Maze (MWM), an open-pool analysis of spatial navigation and reference memory involved in finding a platform, and the Cincinnati Water Maze (CWM), a swimming labyrinth test of an animal's ability to navigate in darkness using route-based internal cues.

Because of widespread use since its development in 1981, Vorhees said, "MWM is the most validated test of hippocampal-dependent spatial learning that exists." He pointed out that there are variations of MWM and CWM that could be used to conduct further evaluation of memory deficits. He also cautioned the audience about potential sex and strain differences in response.

(Sheetal Thakur, Ph.D., is an Intramural Research Training Award fellow in the NTP Toxicology Branch.)



*Shown from above, the CWM is partially filled with water. The length of time it takes a rodent to negotiate the labyrinth, and the number of its errors, can reflect the extent to which learning and memory are affected by the drug or chemical administered. (Photo courtesy of Charles Vorhees)*



*To eliminate distal cues, the CWM is conducted in complete darkness, and monitored with an infrared light emitter and camera. According to the Animal Behavioral Core [website](#), the test provides a method for evaluating an animal's entorhinal cortex, where grid cells integrate information from the hippocampus and the pre- and post-subiculum, where head direction cells are located. (Image courtesy of Charles Vorhees)*

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## Exploratory study first to quantify TCE in breast milk

*By Sarah Wilkinson*

A new [study](#) funded in part by the [NIEHS Superfund Research Program \(SRP\)](#) at the University of Arizona (UA) reports, for the first time, levels of the environmental contaminant trichloroethylene (TCE) in breast milk.

Published Aug. 21 in *Environmental Science and Technology*, the study identified the chemical, which the [U.S. Environmental Protection Agency \(EPA\)](#) has identified as a high priority need for risk assessment, in 35 percent of the breast milk samples analyzed.

"The results of this exploratory study suggest that more in-depth studies will be important for understanding the risk to infants of TCE exposure via breast milk intake and how to reduce the mothers' exposure," said lead researcher [Paloma Beamer, Ph.D.](#), an environmental engineer at the UA Mel and Enid Zuckerman College of

Public Health. In the meantime, the authors stress that mothers should continue to breastfeed their children to ensure critical health benefits for both mother and baby.

### **Bathing water exposes babies to TCE in mothers' milk**

The study sampled breast milk from women in 20 households in Nogales, Ariz., a city known to have TCE-contaminated groundwater. The research team collected samples of water used for drinking, cooking, laundry, and bathing, and administered a risk factor questionnaire. They detected TCE in seven of the 20 breast milk samples, ranging from 1.5 to 6 nanograms per milliliter.

The researchers also found TCE in all water samples collected. The concentration of TCE in breast milk was significantly associated with the concentration of TCE in water used for bathing and laundry, but not drinking and cooking. TCE was more likely to be found in breast milk of mothers whose babies had a body mass index less than 14. Based on average breast milk consumption, the researchers proposed that TCE intake for five percent of infants might exceed the proposed EPA reference dose.

### **TCE as a public health concern**

Used as a solvent, in the past, for many industrial and commercial applications, TCE is the most frequently reported organic contaminant in groundwater and impacts communities across the country. TCE and other chlorinated solvents are the primary contaminants of concern at 31 of 35 state and 13 of 15 federal Superfund sites in Arizona.

In other studies, TCE exposure has been associated with increased risk of a variety of diseases, from autoimmune diseases such as lupus, to blood disorders and cancer. Maternal and early childhood exposures have been associated with increased risk of childhood cancers, such as leukemia.

Nogales, the largest border city in Arizona, is home to a 13-acre TCE plume, and faces a unique potential for additional TCE exposure from rapid growth of industrial production along the US-Mexico border. Nogales was selected as the study site for this project, because of existing TCE contamination and an increased prevalence of lupus and cancers associated with TCE exposure.

In addition to Beamer, the UA SRP research team included Eduardo Sáez, Ph.D., of the UA Department of Chemical and Environmental Engineering; Leif Abrell, Ph.D., of the Arizona Laboratory for Emerging Contaminants; community research partner Swilma Campos, of the Mariposa Community Health Center;



*Beamer, left, and graduate student Luik prepared breast milk samples for analysis. (Photo courtesy of Cassandra Lau, University of Arizona Southwest Environmental Health Sciences Center)*



*A breastfeeding mother and her baby are shown at the study site in Nogales. (Photo courtesy of Swilma Campos, Mariposa Community Health Center)*

María Elena Martínez, Ph.D., of the University of California, San Diego; and Catherine Luik, a recent master of public health graduate of the UA College of Public Health.

The study was also supported by funding from the American Cancer Society, National Cancer Institute, Health Resources and Services Administration, and National Science Foundation.

*Citation:* [Beamer PI](#), [Luik CE](#), [Abrell L](#), [Campos S](#), [Martínez ME](#), [Sáez AE](#). 2012. Concentration of trichloroethylene in breast milk and household water from Nogales, Arizona. *Environ Sci Technol* 46(16):9055-9061.

(Sarah Wilkinson, Ph.D., is the research translation coordinator for the Superfund Research Program at the University of Arizona.)

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## Former Superfund trainee honored for mass spec research

*By Eddy Ball*

Food chemist and toxicologist [Nils Schebb, Ph.D.](#), was honored Sept. 18 for research he conducted as an NIEHS-supported postdoc at the University of California (UC), Davis. The award-winning [study](#), “Investigation of human exposure to triclocarban after showering and preliminary evaluation of its biological effects,” was published in 2011 in *Environmental Science and Technology*.

The section of liquid chromatography mass spectrometry (LC/MS) of the German Society for Mass Spectrometry presented Schebb with the 2012 AB SCIEX LC/MS Award for this work, during its annual workshop at the historic town hall in Wuppertal, Germany. The award included a prize of 3,000 euro, funded by the company [AB SCIEX](#), a major producer of MS systems for a host of applications, including drug discovery, clinical research, food production, and toxicology.

From 2009 to 2011, Schebb was a member of the UC Davis [Laboratory of Pesticide Biotechnology](#), headed by veteran NIEHS grantee Bruce Hammock, Ph.D., prior to forming his own group in the Institute for Food Toxicology and Chemical Analysis at the University of Veterinary Medicine Hannover in Hannover, Germany. Schebb’s award-winning study was one of 15 toxicological and laboratory methods papers he has co-authored on work with the Hammock group.



*Schebb is a prolific scholar who has co-authored 24 PubMed indexed publications. (Photo courtesy of Nils Schebb)*

### Improved sensitivity and analytical throughput

To assess human exposure to the persistent and widely used antibacterial soap additive triclocarban (TCC), Schebb and his co-authors developed and validated a sensitive online solid-phase extraction (SPE) LC/MS. Unlike earlier approaches, the new method is capable of rapidly analyzing the compound and its major metabolites in urine and other complex biological samples.

The study referenced recent findings indicating that TCC is persistent in the aquatic environment and has significant off-target biological activity. In order to assess potential biological effects arising from TCC exposure, the researchers screened the compound for effects on human enzymes *in vitro*.

One result of special interest to the group was evidence that TCC strongly inhibits the enzyme soluble epoxide hydroxylase (sEH), suggesting that exposure could impact human health. Hammock and his group have published a series of studies on the efficacy of sEH suppression in the regulation of blood pressure, inflammation, and pain. A preliminary followup study with rats failed to replicate the *in vitro* results systemically *in vivo*, although the team could not rule out local dermal effects that might be significant.

In their experiments, Schebb and his co-authors identified urinary glucuronides as a sensitive marker of TCC, and found sufficient evidence of biological activity to justify follow-up studies.

“Long-term exposure studies in humans, that include biomonitoring of TCC in blood, should be carried out to evaluate if exposure after using personal care products, containing up to 1.5 percent TCC, provides a sufficient margin of safety,” they concluded. “With the online-SPE-LC/MS method described herein, we provide an excellent analytical tool to answer these questions.”

Since the publication of the 2011 study, Schebb has been involved in five [follow-up studies](#) on TCC, as part of his research on bioactivity and pharmacokinetics of food ingredients and environmental contaminants.

*Citation:* [Schebb, NH, Inceoglu B, Ahn KC, Morisseau C, Gee SJ, Hammock BD](#). 2011. Investigation of human exposure to triclocarban after showering and preliminary evaluation of its biological effects. *Environ Sci Technol* 45(7):3109-3115.

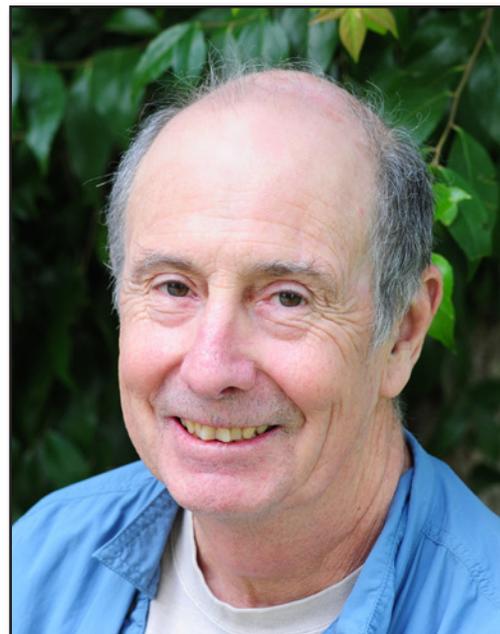
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## Paraoxonases — poster-children for gene-environment interactions

By *John House*

Veteran NIEHS grantee [Clement Furlong, Ph.D.](#), a leading researcher in the study of insecticide metabolism and professor of genome sciences and medicine at the University of Washington’s School of Medicine, visited NIEHS Sept. 4. Furlong’s presentation, “The Many Facets of Gene-Environmental Interactions of the Paraoxonases,” was hosted by Superfund Research Program Administrator [Danielle Carlin, Ph.D.](#)

Furlong shared the work his group and others have been conducting on the paraoxonase (PON) family of genes that are involved in the detoxification of pesticide metabolites and other toxicants, with a focus on how variation in PON genes influences disease susceptibility. Furlong has experimented with ways to manipulate levels of PON proteins as a treatment and prevention strategy and translated his findings into screening tests to improve worker and public safety, as well as potentially advance personalized medicine.



*Hammock’s research interests range across omics platform development, pest control, and drug development. He has been honored for his teaching and mentoring, as well as for his groundbreaking scientific research. (Photo courtesy of Bruce Hammock)*

## PON1 and organophosphate compounds

The first physiological function of PON1 Furlong examined was its detoxification of organophosphate (OP) compounds. Cytochrome P450 enzymes replace the P=S bond with the more toxic P=O (oxon) bond that binds acetylcholine esterase (AChE) leading to increased ACh and subsequent nervous system toxicity. PON1 exerts neuroprotective effects by hydrolyzing oxons.

As Furlong noted, “Early in the [NIEHS Environmental Genome Project](#), PON1 was cited as an excellent example of gene-environment interaction,” and his subsequent research has born this out. PON1 has many identified single nucleotide polymorphisms (SNPs) that have been characterized. For example, the SNP at -108C results in twice the levels of plasma PON1 over -108T. In addition, the Q192R SNP results in greater catalytic efficiency of PON1. This effect is important given that PON1-Q192, which is less protective, exists in homozygous state for up to 50 percent of some populations.

Additional experiments in his lab, he explained, provided very solid evidence that high levels of paraoxonase were protective against OP exposure, specifically oxon exposure. Major breakthroughs in understanding the function of PON1 came from the PON1 humanized mice generated at the University of California, Los Angeles by Diana Shih, Ph.D., Jake Lusic, Ph.D., and Aaron Tward, Ph.D. By creating PON1 knockout mice and then inserting a transgene coding for the human forms of PON1 with the Q192 and R192 alleles, they demonstrated conclusively the variability in organophosphate toxicity, oxon metabolism and AChE activity between Q192 and R192 alleles.

Additional humanized mouse experiments by Furlong’s group have partially explained the heightened sensitivity observed in young animals and humans to OP insecticides such as chlorpyrifos and diazinon. The levels of plasma PON1 are low at birth and increase over the developmental time period in mice, postnatal day 21, and humans, postnatal year two. When human PON1 transgenes are expressed in mice, they undergo the same developmental time course of expression as endogenous mouse PON1.

## PONs and human health

One of the holy grails of genomic research is individually tailored or personalized medicine, which requires accurate and economically feasible functional assays. Furlong’s group has developed a two-substrate



*Furlong pointed to how genetic differences can make travelers more susceptible to the effects of exposure to aircraft engine lubricant fumes in cabin air. (Photo courtesy of Steve McCaw)*



*Carlin’s research interests include cardiopulmonary and reproductive physiology and inhalation toxicology and pharmacology. (Photo courtesy of Steve McCaw)*

arylesterase assay that is able to differentiate between high and low PON1 activity and subsequent OP toxicity susceptibility. This development has assisted the State of Washington's BChE (Butyrylcholinesterase or plasma cholinesterase) agricultural worker monitoring program in determining OP poisoning susceptibility.

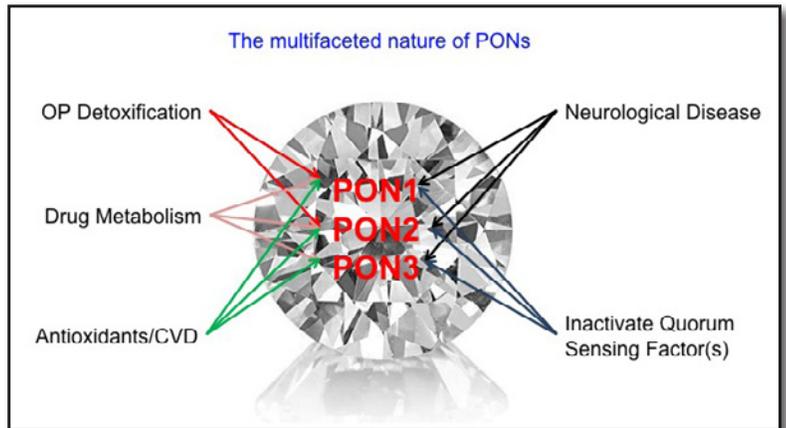
Recent work by a postdoctoral fellow in Furlong's group, Judit Marsillach, Ph.D., and Ed Hsieh, Ph.D., a postdoctoral fellow with the research team led by Mike MacCoss, Ph.D., has allowed determination of OP exposure with a single blood draw by measuring the percent modification of the active site serine of BChE by OP adducts, thus obviating the requirement for a pre-spray season blood draw. In addition, Furlong's group has also made progress modifying the PON1 protein for greater efficiency to treat OP poisoning. Furlong closed his talk on the gene-environment interactions of paraoxonases by stressing that epidemiological studies related to the role of genetic variability in PON1 to risk of exposure or disease must include measures of activity to be useful.

(John House, Ph.D., is a postdoctoral fellow in the NIEHS Genetics, Environment, and Respiratory Disease Group.)

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*Furlong's presentation attracted a capacity audience of scientists from NIEHS and elsewhere, including NIEHS leadership, such as Pat Mastin, Ph.D., above, the deputy director of the Division of Extramural Research and Training, and NIEHS/NTP Director Linda Birnbaum, Ph.D. (Photo courtesy of Steve McCaw)*



*PON genes have been characterized in a variety of unique roles.*

## Kunkel delivers keynote at Gordon conference on mutagenesis

*By Jeffrey Stumpf*

NIEHS scientists and grantees convened with internationally renowned scientists in Newport, R.I., for the [2012 Mutagenesis Gordon Research Conference \(GRC\)](#). Leading the way, Laboratory of Structural Biology head [Thomas Kunkel, Ph.D.](#), delivered the keynote address about his research on the biological processes that are affected by incorporating ribonucleotides into DNA.

Processes that promote inaccurate DNA replication and mutations affect human health and survival. Genome integrity results from a delicate balance between the potential toxicity of DNA damaging agents and cellular processes that repair the damage and restore replication.

Many presentations discussed how DNA repair pathways are overwhelmed in aging, various cancers, and genetic disease, which is of interest to former NIEHS postdoctoral research fellow [Janine Santos, Ph.D.](#)

“I’m particularly fascinated with how DNA repair proteins safeguard genome integrity, both in the nucleus and mitochondria,” Santos explained. “There is quite a wide range of disease symptoms associated with failure of DNA repair systems.”

### Where RNA meets DNA

The five-day, biennial conference continues a long-standing tradition in the field of DNA replication and repair. Attending his 16th Mutagenesis GRC, Kunkel argues that new discoveries in DNA damage tolerance and repair maintain the persistent interest in mutagenesis.

“The studies of mutagenesis continue to thrive, because mutations are fundamental to so many aspects of biology, with profound implications on topics from evolution to human health,” Kunkel noted.

Kunkel’s keynote talk showcased an important new line of investigation in mutagenesis — uncovering unexpected consequences for incorporating ribonucleotides into DNA. Kunkel’s research shows that ribonucleotides, while normally considered as the building blocks of RNA, exist in DNA much more prevalently than any other DNA damage or abnormal nucleotide. Kunkel believes that this observation is biologically important, and the field agrees.

“This meeting showcased several talks and posters showing previously unanticipated overlap between transactions involving DNA and RNA,” Kunkel said.

The intersection of DNA and RNA was evident in research connected to NIEHS. Former NIEHS postdoc and current assistant professor at the Georgia Institute of Technology, [Francesca Storici, Ph.D.](#), discussed repair pathways that are mediated by RNA. Current NIEHS grantee, [Paul Doetsch, Ph.D.](#), of the Emory University School of Medicine, described his research on how transcription can succumb to many of the same problems as DNA replication, in regard to damage and mistakes.

### Celebrating diversity of DNA structure and functions

While the conference highlighted the newest insights on DNA damage responses, various talks emphasized the variety of types of DNA in the cell. The second keynote lecture, by Rockefeller University professor [Titia de Lange, Ph.D.](#), addressed how telomeres, the noncoding ends of chromosomes, maintain overall genome stability. The contrast in Kunkel’s and de Lange’s research underscored the conference’s emphasis on including work beyond classical mutagenesis research. [Patricia Opresko, Ph.D.](#), assistant professor at the University of Pittsburgh and an NIEHS Outstanding New Environmental Scientist (ONES) grant awardee, appreciated the multifaceted approach.



*During his keynote speech, Kunkel briefly summarized the variety of subjects covered in the five-day meeting. “In regard to DNA replication, there are a lot of ways to do things wrong.” (Photo courtesy of Steve McCaw)*



*Santos is an assistant professor at the University of Medicine and Dentistry of New Jersey (UMDNJ) and is currently working as a guest researcher in the Laboratory of Toxicology and Pharmacology at NIEHS. (Photo courtesy of UMDNJ)*

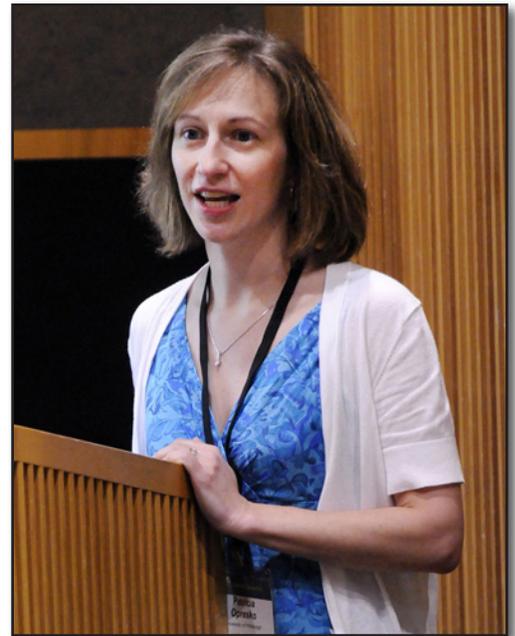
“These talks beautifully demonstrated how important advances are made by maintaining cutting-edge research in more familiar topics, like DNA polymerase fidelity,” Opresko mentioned, “but also by extending mutagenesis research to related fields of telomere biology.”

Several talks, based on research funded by NIEHS, reflected the diversity in the role of mutagenesis in human health. For instance, ONES awardee [Sarah Delaney, Ph.D.](#), discussed DNA damage in expansion of triplet repeats that are prevalent in diseases such as Huntington’s disease. Fellow grantee [Myron Goodman, Ph.D.](#), presented one of several talks on specific kinds of mutagenesis that are necessary for antibody production.

Emerging technologies, such as deep sequencing, have promoted some of the depth and variety of research in DNA mutagenesis. The trend of exciting new discoveries in mutagenesis and their links to human health motivated several in the field to mark the 2014 Mutagenesis GRC on their calendars.

“With the advent of so many powerful new technologies that truly amaze me, I’ve never been more optimistic for the future of this field than I am right now,” Kunkel remarked.

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



*With a special interest in de Lange’s keynote address, Opresko is intrigued with how DNA damage is repaired at telomeres. (Photo courtesy of Steve McCaw)*



*Conference attendees congregate on the lawn of Salve Regina University, adjacent to the picturesque Cliff Walk in Newport. Chair and vice chair of this year’s conference, front center, were Bruce Demple, Ph.D., left in black t-shirt, and Robert Lahue, Ph.D. (Photo courtesy of Michael Salerno from Michael Salerno Photography)*

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# Study finds that dad's job can influence birth defects

By Nancy Lamontagne

Although emphasis is often placed on how pregnant women can increase their chances of having a healthy infant, a large population [study](#) shows that men also play a role in their unborn child's health. The new NIEHS-funded study found that men who worked in certain occupations, around the time of conception, were more likely to father offspring with various birth defects.

Epidemiologist Tania Desrosiers, Ph.D., of the University of North Carolina at Chapel Hill Gillings School of Global Public Health, led the research team. Although the study didn't measure workplace exposures, the findings can be used to generate hypotheses about specific occupations and exposures for future research that incorporates exposure assessment.

The investigators looked for associations between paternal occupation and birth defects, using data from the [National Birth Defects Prevention Study](#), which included 9,998 fathers of children with one or more birth defects, and 4,066 fathers of children without birth defects. Many previous studies on this topic have grouped occupations with varied exposures, but the new study individually examined more than 60 types of occupations.

"We examined nurses, dentists, and physicians, separately, which is important given that different exposures are encountered at each of these jobs," said Desrosiers, a former NIEHS predoctoral trainee.

"Likewise, we also considered over 60 types of distinct birth defects, whereas previous studies have often lumped together various defects, such as all heart defects, that may affect the same anatomic region, but are considered to have different etiologies."

## Job categories with increased birth defects

After considering other risk factors, such as education level, vitamin use, smoking, alcohol intake, and maternal age, race, and ethnicity, the researchers found an increased occurrence of various birth defects in several job categories. The occupations include mathematical, physical, and computer scientists; artists; photographers and photo processors; food service workers; landscapers and groundskeepers; hairdressers and cosmetologists; office and administrative support workers; sawmill workers; petroleum and gas workers; chemical workers; printers; material moving equipment operators; and motor vehicle operators.

Specifically, photographers and photo processors were more likely to father children with congenital abnormalities of the eye, while landscapers and groundskeepers were more likely to father children with gastrointestinal defects.

"We don't advise fathers-to-be to change jobs, but it may be prudent to reduce or avoid unnecessary exposure to potentially harmful agents in the workplace," Desrosiers said. "More research is needed to elucidate whether specific exposures found in the workplace, such as exposure to organic solvents or pesticides, for example, might account for the observed relation between particular jobs and birth defects."



*Desrosiers cautions that, although her team observed modest increases in the risk of birth defects among children of fathers with certain types of jobs, the absolute increase in risk is still small, because birth defects are rare in the general population. (Photo courtesy of Tania Desrosiers)*

Since the study identified an increased risk of birth defects among children of fathers with several occupations that likely involve exposure to organic solvents, the researchers plan to investigate whether paternal solvent exposure is associated with birth defects, using data from a retrospective occupational exposure assessment performed on a subset of these fathers.

In addition to the NIEHS funding, the study was also supported by the Centers for Disease Control and Prevention.

*Citation:* Desrosiers TA, Herring AH, Shapira SK, Hooiveld M, Luben TJ, Herdt-Losavio ML, Lin S, Olshan AF, National Birth Defects Prevention Study. 2012. Paternal occupation and birth defects: findings from the National Birth Defects Prevention Study. *Occup Environ Med.* 69(8):534-542.

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

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## Novel technique for determining DNA damage effects on gene transcription

By Sheila Young

A new study funded in part by NIEHS may make it possible to determine exactly how a particular DNA lesion alters transcription and gene expression, more quickly and accurately than previously possible. Published online Aug. 19 by *Nature Chemical Biology*, the study was conducted by Outstanding New Environmental Scientist (ONES) awardee Laura Niedernhofer, M.D., Ph.D., a team from the University of California, Riverside, and a researcher from the National Institute on Alcohol Abuse and Alcoholism, describing a new competitive transcription and adduct bypass (CTAB) assay.

[Niedernhofer](#), who was on the faculty of the University of Pittsburgh when the paper was submitted, is currently an associate professor in the Department of Metabolism and Aging at the Jupiter, Fla. Campus of the Scripps Research Institute.



*Niedernhofer hopes that a better understanding of the genome-level mechanisms in aging will ultimately lead to preventive strategies. (Photo courtesy of Laura Niedernhofer)*

“This is a really important line of investigation,” Niedernhofer said of the study. “Most cells in the body are post-mitotic, meaning that they don’t replicate their genome and divide. In these cells, it is of greater concern how an RNA polymerase copes with DNA damage during transcription than a DNA polymerase during replication. We simply don’t know much about the impact of DNA damage on transcription.”

### Direct measurement of altered transcripts

When Niedernhofer visited NIEHS in July, she discussed her research on the relationship between DNA damage and aging in a seminar that attracted some of the top researchers at the Institute ([see related story](#)). Her research showed that the heterodimeric nuclease ERCC1-XPF promotes efficient DNA damage repair, which is crucial in preventing premature aging. She also discussed her study on the activation of NF-kb in response to DNA damage during accelerated and normal aging, which was published in the July issue of the *Journal of Clinical Investigation*.

According to Niedernhofer, current techniques for measuring perturbations in the transcription of a lesion-containing DNA template often involve extensive DNA sequencing and colony screening procedures, and do not directly prove that DNA damage alters transcription. The new CTAB assay, on the other hand, enables researchers to quantitatively determine how site-specific DNA lesions affect the efficiency and fidelity of gene transcription. This assay is more efficient since it omits the exhaustive screening steps that most existing protocols require. More importantly, it enables a more accurate identification of mutant transcripts via the use of liquid chromatography and mass spectrometry.

### **Insights into damage recognition and DNA repair linked to aging**

This new technique measures the degree to which a specific DNA adduct inhibits transcription by calculating a relative bypass efficiency (RBE) value. This value represents the ability of an RNA polymerase or cell to polymerize RNA through a damaged DNA template base to complete gene transcription; the higher the RBE values, the better the cells are at ignoring the damage and carrying on with their job of making mRNA. In this study, the researchers examined how DNA adducts affect transcription. These adducts arise in the mammalian genome as a result oxidative insults, exposure to environmental contaminants, and normal physiological processes. If left unrepaired, they contribute to various cancers, health complications, and aging.

The key findings of the study were that several of these oxidative DNA lesions, which are abundant in our bodies, are strong inhibitors of transcription in mammalian cells, including N2-CEDG, S-cdA, and S-cdG. In addition, several lesions caused the polymerases to make mistakes and introduce mutations into the transcript, including S-cdA and S-cdG. These findings provide novel evidence that DNA damage can have profound effects even on non-replication cells, potentially leading to production of fewer or erroneous proteins.

Niedernhofer and her colleagues conclude that future work should be aimed at expanding the repertoire of lesions studied in the CTAB assay to discover the effects of environmental genotoxins and chemotherapeutic agents on transcription and non-dividing cells.

*Citation:* You C, Dai X, Yuan B, Wang J, Wang J, Brooks PJ, Niedernhofer LJ, Wang Y. 2012. A quantitative assay for assessing the effects of DNA lesions on transcription. *Nat Chem Biol*: doi: 10.1038/nchembio.1046 [Online 19 August 2012].

(Sheila Yong, Ph.D., is a visiting fellow in the NIEHS Laboratory of Signal Transduction.)

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## **Low dose experts gather in Berlin**

*By Thaddeus Schug*

NIEHS/NTP Director Linda Birnbaum, Ph.D., welcomed risk assessors, toxicologists, endocrinologists, and epidemiologists to the “Low Dose Effects and Non-Monotonic Dose Responses for Endocrine Active Chemicals: Science to Practice” workshop Sept. 11 in Berlin with a video presentation. The workshop was co-organized by NIEHS Health Scientist Administrator Jerry Heindel, Ph.D., and Sharon Munn, European Commission Joint Research Centre and Institute of Health and Consumer Protection (JRC-IHCP) representative, along with a committee of scientists from U.S. and European government agencies.

“One of the environmental factors that NIEHS is investing significant resources in is research on endocrine disruptors. We want to be sure that the high quality data generated by our in-house researchers and our grantees,

is useful in the risk assessment process,” said Birnbaum. “We are very interested in your views as to the strength of the data supporting low dose effects and non-monotonic dose responses for chemicals with endocrine disrupting properties,” added Birnbaum.

**Linked video:**  
 Watch Birnbaum's recorded address to attendees at the Berlin workshop (05:05)  
 (Launches in new window)

Download Media Player: Flash

Birnbaum noted that an increasing number of studies suggest that low doses are unsafe, even for populations who are not usually considered vulnerable. “Studies continue to show associations between the concentrations of these chemicals in the general population and adverse health effects, such as obesity, type-2 diabetes, reduced fertility, neurobehavioral disorders, and immune dysfunction,” she told the audience.

### State of the science on endocrine-active substances

The workshop brought together nearly 200 scientists to discuss whether current scientific evidence on low dose effects and non-monotonic dose response curves for endocrine-active substances is sufficient to re-examine the ways in which chemicals are tested and assessed for human health effects.

The meeting began with representatives from the academic community laying out the principles of endocrinology and evidence for the existence of non-monotonic dose responses and effects at low doses. These presentations were followed by experts from the risk assessment community detailing current risk assessment approaches and the possible implications for risk assessment and approaches to toxicity testing, if effects could be expected at environmentally relevant human exposure levels from substances acting via disruption of the endocrine system. There were then two separate breakout groups to discuss various aspects of the topics.

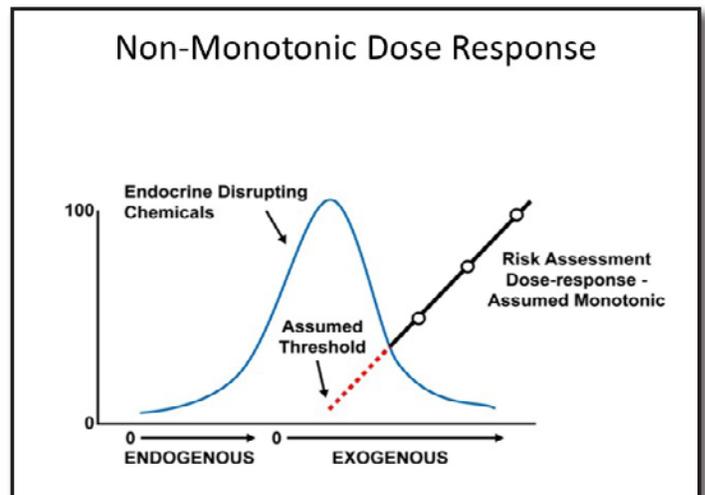
### Drawing conclusions

According to Heindel, while there was not a consensus, many of the workshop participants were in agreement that non-monotonic dose responses do occur and these effects may be expected at some dose ranges for select chemicals. However, the extent to which adverse low dose responses might occur was considered to be a separate issue and was not as highly supported. Participants agreed that a more rigorous definition of low dose would be helpful as the term is not currently used consistently among toxicologists. There was also general agreement for a need to carry out a practical assessment of the type of effects that may be considered adverse in the context of endocrine disruption.

### Potential Low Dose Health Effects

- Reproductive dysfunction
- Cancers
- Immune dysfunction
- Metabolic disorders
- Brain development changes
- Behavioral changes
- Cardiovascular disease

*Endocrine signals govern every organ and process in the body. This means that when chemicals interfere with endocrine signaling, the effects can be seen in many different conditions and diseases. (Image courtesy of Jerry Heindel)*



*Heindel used the diagram in his presentation. “Some agents, such as endocrine disruptors, have a substantial impact on our health even at very low doses,” he explained. “For some endocrine disruptors, biological changes can be seen at low doses, but not at high doses.” (Image courtesy of Jerry Heindel)*

Some recommendations from the workshop include developing guidance on minimum data requirements for the publication of studies investigating endocrine disrupting activity so the data would be more useful for risk assessments, developing methods for data sharing, and creating a knowledge base for compiling findings of non-monotonic dose response relationships. There was also considerable discussion about ways that test guidelines might be augmented and evaluated with respect to detecting low-dose effects or non-monotonic dose responses.

The meeting was hosted in Berlin by Germany's Federal Environment Agency and the Charité Medical University of Berlin. Other sponsors of the workshop included the Danish Ministry of the Environment, Danish Technical University's National Food Institute, French Agency for Food, Environmental and Occupational Health (ANSES), and the Oak Foundation.

(Thaddeus Schug, Ph.D., is a health scientist in the NIEHS Division of Extramural Research and Training and a regular contributor to the Environmental Factor.)



*Workshop organizers took center stage in the lecture hall during a break in proceedings. Shown, left to right, are Maurice Whelan, Ph.D., and Munn, of JRC-IHCP; Heindel; and Gilbert Schoenfelder, M.D., of Charité Medical University of Berlin, Institute of Clinical Pharmacology and Toxicology. (Photo courtesy of the European Commission)*

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## This month in EHP

For its annual Children's Health issue, [Environmental Health Perspectives \(EHP\)](#) highlights new research on how assisted reproductive technologies and epigenetics impact development.

### **Altering the Primal Environment: Health Effects Associated with Assisted Reproductive Technologies**

Assisted reproductive technologies involve the use of fertility drugs and the manipulation of eggs and sperm in a laboratory setting. Since the first test tube baby was born in 1978, investigators have studied whether these interventions set the stage for adverse health outcomes in children. The evidence to date indicates most artificially conceived babies are born perfectly healthy, although long-term health effects have yet to be fully investigated.

### **A Steep Learning Curve: Decoding Epigenetic Influences on Behavior and Mental Health**

Of the thousands of epigenetics studies published in the past two decades, a few hundred have addressed behavioral and mental health outcomes, but only a fraction of those have dealt with fetal or childhood exposures or outcomes. However, early results in the niche field of behavioral epigenetics suggest such studies could provide insights into a variety of behavioral and mental health conditions.

### **Podcast — Post-Katrina Asthma in the Children of New Orleans, with Patricia Chulada**

New Orleans is already known as a hot, moist place — ideal growing conditions for mold. Now factor in Hurricane Katrina, which hit the city in August of 2005, leaving behind even more indoor mold and other asthma-causing allergens. In this month's [Researcher's Perspective](#) podcast, host Ashley Ahearn talks with Patricia Chulada, Ph.D., about her work studying post-Katrina asthma symptoms in the children of New Orleans and implementing a new asthma counselor intervention in a large NIEHS-funded initiative ([see story](#)).

Featured commentaries, reviews, and research this month include:

- Predicting Later-Life Outcomes of Early-Life Exposures
- Rice Consumption and Arsenic in U.S. Children
- 450K Epigenome-Wide Scan: DNA Methylation in Newborns of Smoking Mothers
- Metal Exposures in Child Laborers
- Surrounding Greenness and Pregnancy Outcomes

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<http://twitter.com/ehponline>



# Upcoming workshop on innovative safety tests for pertussis vaccines

By Debbie McCarley and Cathy Sprankle

NIEHS and U.S. Food and Drug Administration (FDA) scientists will join other scientific experts from around the world this fall to consider improved methods and approaches for safety testing of vaccines that protect against pertussis. The “International [Workshop](#) on Alternatives to the Murine Histamine Sensitization Test (HIST) for Acellular Pertussis Vaccines: State of the Science and the Path Forward” will take place on Nov. 28-29 at the William H. Natcher Conference Center on the NIH campus in Bethesda, Md.

The NTP Interagency Center for the Evaluation of Alternative Toxicological Methods ([NICEATM](#)) is organizing the workshop in collaboration with the Interagency Coordinating Committee on the Validation of Alternative Methods ([ICCVAM](#)) and partner organizations in the [International Cooperation on Alternative Test Methods](#). The organizing committee for the workshop includes NIEHS scientists and scientists from the FDA, international vaccine manufacturers, and international research and regulatory agencies.



**Linked video:**  
[Watch as President of the National Foundation of Infectious Diseases William Schaffner, M.D., discusses why pertussis vaccine development and safety testing need to continue \(01:11\)](#)

Download Media Player:  Flash 

## Pertussis is an important public health concern

Pertussis, also known as whooping cough, is a highly contagious bacterial disease that was once a major cause of childhood mortality. While widespread vaccination has substantially decreased the incidence of pertussis, recent outbreaks have led public health officials to recommend renewed and expanded vaccination efforts. For example, a sharp increase in the number of pertussis cases in early 2012, in central North Carolina, prompted the state health department to offer free pertussis vaccinations.

Regulatory authorities require testing of each production lot of a vaccine to ensure safety, potency, and purity. The murine HIST is a key safety test performed on pertussis vaccines to ensure that residual pertussis toxin has been effectively inactivated, to avoid adverse effects caused by the toxin. However, such testing requires large numbers of mice, some of which experience significant unrelieved pain and distress. An international [workshop](#) in 2010 identified the HIST as a priority for future research, development, and validation of alternative test methods that could reduce, refine, or replace animal use for pertussis vaccine safety testing.



**International Workshop on Alternatives to the Murine Histamine Sensitization Test (HIST) for Acellular Pertussis Vaccines: State of the Science and the Path Forward**

**November 28–29, 2012**  
**William H. Natcher Conference Center**  
**National Institutes of Health**  
**Bethesda, Maryland, USA**

**Organized by members of the International Cooperation on Alternative Test Methods:**  
**NICEATM** National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods  
**ICCVAM** Interagency Coordinating Committee on the Validation of Alternative Methods  
**EURL ECVAM** European Union Reference Laboratory for Alternatives to Animal Testing  
**JaCVAM** Japanese Center for the Validation of Alternative Methods  
**KoCVAM** Korean Center for the Validation of Alternative Methods  
**Health Canada**

**For more information and to register, please contact NICEATM:**  
<http://iccvam.niehs.nih.gov/> — (919) 541-2384 — [niceatm@niehs.nih.gov](mailto:niceatm@niehs.nih.gov)

Individuals with disabilities who need accommodation to participate in this event should contact Debbie McCarley at 919-541-2384 or [mccarley@niehs.nih.gov](mailto:mccarley@niehs.nih.gov). TTY users should contact the Federal TTY Relay Service at 800-877-8339. Requests should be made at least 5 days in advance of the event.

**ICCVAM Agencies:**

- Agency for Toxic Substances and Disease Registry
- Consumer Product Safety Commission
- Department of Agriculture
- Department of Defense
- Department of Energy
- Food and Drug Administration
- National Cancer Institute
- Department of Transportation
- National Institute for Occupational Safety and Health
- National Institute of Environmental Health Sciences
- National Institutes of Health
- National Library of Medicine
- Department of the Interior
- Occupational Safety and Health Administration
- Environmental Protection Agency

Photomicrograph courtesy of Jeffrey Garcia, PhD, Department of Pediatrics, University of North Carolina School of Medicine.  
Line graph courtesy of U.S. Centers for Disease Control and Prevention.  
Microscopic photograph courtesy of James Galbraith II, Centers for Disease Control and Prevention.



“There is significant international interest in supporting innovation in this area,” notes Rear Adm. William Stokes, D.V.M., director of NICEATM, which administers and provides scientific support for ICCVAM. “In addition to animal welfare concerns, the HIST is time-consuming and technically challenging. Both vaccine manufacturers and regulators are actively working to develop and validate improved alternatives that can achieve acceptance and use.”

The ICCVAM Authorization Act of 2000 charges ICCVAM with coordinating the interagency evaluation of new testing methods that can replace or reduce the use of animals, and refine animal use to enhance animal well-being and lessen or avoid pain and distress. Vaccine testing uses significantly more animals, and results in more animals experiencing pain and distress than toxicity testing. Therefore, promoting improved alternative test methods for vaccine potency and safety testing is one of the highest priorities in [ICCVAM’s five-year plan](#).

### About the workshop

The upcoming workshop will provide a forum for participants to review protocols and available data from an ongoing international study of *in vitro* alternatives to the HIST. Participants will also review recent advances and innovations in science and technology that may provide greater accuracy, precision, and efficiency, and that are more humane and use fewer or no animals. Finally, the workshop will address the path to achieve validation, global acceptance, and implementation of new alternative methods.

Registration information and a workshop program are available on the [NICEATM-ICCVAM website](#). NICEATM and ICCVAM also invite the submission of abstracts for scientific posters to be displayed during this workshop. Abstracts should be submitted by Oct. 12.

Stokes and Warren Casey, Ph.D., deputy director of NICEATM, are serving on the organizing committee for the workshop. The committee also includes Richard McFarland, Ph.D., M.D., co-chair of the ICCVAM Interagency Biologics Working Group, Juan Arciniega, D.Sc., and Lev Sirota, Ph.D., all from the FDA Center for Biologics Evaluation and Research.

(Debbie McCarley is a special assistant to Stokes. Cathy Sprankle is a communications specialist with ILS, Inc., support contractor for NICEATM.)

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## Workshop on human genomic plasticity begins Oct. 4

By Eddy Ball

An innovative interagency program continues its 2012 workshop series with an exploration of “[Exploring Human Genomic Plasticity and Environmental Stressors: Emerging Evidence on Telomeres, Copy Number Variation, and Transposons](#)” Oct. 4-5 in Washington, D.C.



The workshop, which is part of the National Academies Emerging Science for Environmental Health Decisions series, is free and open to the public. [Registrations](#) for onsite attendance and webcast access are now being accepted.

## Genomic plasticity triggered by environmental exposures

Genomes have the characteristic of plasticity, which makes it possible to adapt quickly in order to survive changes in environmental conditions. Along with epigenetic modifications, mobile and evolving elements, such as telomeres, transposons, and copy number variants, are important factors in understanding the potential effect of our environment on human health.

Sponsored by NIEHS, the program holds three workshops per year on the use of new discoveries, tools, and approaches for guiding environmental health decisions. The workshops provide a public venue for communication among government, industry, environmental groups, and the academic community.



**Linked video:**  
[Register to watch the archived webcast videos of the June 14-15 workshop on Systems Biology — Informed Risk Assessment](#)  
(Launches in new window)

Download Media Player:  Flash 

The October workshop is the twelfth in the [series](#), which began in July 2009 with a workshop on “Use of Emerging Science and Technologies to Explore Epigenetic Mechanisms Underlying the Developmental Basis for Disease.” Past presentations are archived online, and videos are available for several recent workshops.

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## Extramural papers of the month

By *Nancy Lamontagne*

- [Triclosan impairs heart and skeletal muscle contractility](#)
- [Pan-fried red meat increases risk for prostate cancer](#)
- [Uncovering a defective gene’s role in autism-type behaviors](#)
- [Infant exposure to specific molds linked with asthma risk](#)



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

## Triclosan impairs heart and skeletal muscle contractility

NIEHS grantees report that triclosan hinders muscle contractions at a cellular level and also causes muscle problems in fish and mice. Triclosan is an antibacterial agent widely used in personal-care products such as hand soap and toothpaste, and it has been detected in waterways and fish. This new study provides evidence of the chemical’s potentially negative effects on human and environmental health and also reveals a mechanism for these effects.

The researchers evaluated the effects of triclosan on muscle cells. The triclosan interrupted normal communication between two proteins that function as calcium channels, causing skeletal and cardiac muscles to fail.

In animal studies, anesthetized mice had up to a 25-percent reduction in heart function measures within 20 minutes of exposure to the chemical. Mice given a single dose of triclosan showed an 18-percent reduction in grip strength for up to 60 minutes. The investigators also studied the effects of triclosan exposure on fathead minnows, a model organism used to study the effects of aquatic pollutants. Minnows exposed to triclosan in the water for seven days showed significantly reduced swimming activity compared to controls.

*Citation:* Cherednichenko G, Zhang R, Bannister RA, Timofeyev V, Li N, Fritsch EB, Feng W, Barrientos GC, Schebb NH, Hammock BD, Beam KG, Chiamvimonvat N, Pessah IN. 2012. Triclosan impairs excitation-contraction coupling and Ca<sup>2+</sup> dynamics in striated muscle. *Proc Natl Acad Sci U S A* 109(35):14158-14163.

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## **Pan-fried red meat increases risk for prostate cancer**

An NIEHS grantee and her colleagues found that consuming more than 1.5 servings of pan-fried red meat per week is associated with an increased risk for prostate cancer. The findings point to carcinogens that accumulate in meats cooked at high temperatures as potential risk factors for prostate cancer.

The researchers examined data from nearly 2,000 men with and without prostate cancer. They looked at whether consuming various red meats, processed meats, and poultry was associated with an increased risk of prostate cancer. They took into account cooking methods, meat doneness, and estimated levels of carcinogens.

The study showed that men who consumed more than 1.5 servings of pan-fried red meat per week increased their risk of advanced prostate cancer by 30 percent, and eating 2.5 servings of red meat per week cooked at high temperatures increased risk 40 percent. Of the red meats studied, hamburgers, but not steak, were linked to an increased risk of prostate cancer, especially among Hispanic men. Men with diets high in baked poultry had a lower risk of advanced prostate cancer, while consumption of pan-fried poultry increased risk.

The researchers say that if future studies replicate their findings, then guidelines would be useful for helping the public understand how to cook meat in a way that reduces these carcinogens.

*Citation:* Joshi AD, Corral R, Catsburg C, Lewinger JP, Koo J, John EM, Ingles S, Stern MC. 2012. Red meat and poultry, cooking practices, genetic susceptibility and risk of prostate cancer: results from the California Collaborative Prostate Cancer Study. *Carcinogenesis*; doi: 10.1093/carcin/bgs242 [Online 20 July 2012].

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## **Uncovering a defective gene's role in autism-type behaviors**

A defective *pten* gene can lead to disruptions in the activity of neuronal mitochondria and autism-type behaviors in mice, according to a new study from NIEHS grantees. *Pten* is defective in some children with autism, and this new insight into how the gene affects the brain could lead to new drug targets.

To investigate the effects of a defective *pten* gene, the researchers studied mice with neurons containing only one copy of the gene, rather than the normal two. By four to six weeks after birth, the neurons of these mice showed malfunctioning mitochondria. At 20 to 29 weeks, the researchers observed a dramatic increase in DNA damage and mitochondrial dysfunction. The mice also began to avoid their littermates and engage in repetitive grooming, behaviors associated with autism. Mice with two copies of the *pten* gene did not have malfunctioning mitochondria or behavioral problems.

The researchers also found that defective *pten* interacted with the *p53* gene to impair mitochondrial function in mice. This led to an increase in mitochondrial DNA damage and abnormal levels of energy production in the cerebellum and hippocampus, brain regions that are critical for social behavior and cognition.

*Citation:* Napoli E, Ross-Inta C, Wong S, Hung C, Fujisawa Y, Sakaguchi D, Angelastro J, Omanska-Klusek A, Schoenfeld R, Giulivi C. 2012. Mitochondrial dysfunction in *pten* haplo-insufficient mice with social deficits and repetitive behavior: interplay between *pten* and *p53*. PLoS One 7(8):e42504; doi:10.1371/journal.pone.0042504 [Online 10 August 2012].

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## Infant exposure to specific molds linked with asthma risk

A new NIEHS-supported study provides evidence that infants exposed to three types of mold during infancy have an increased risk of developing asthma during childhood. Since the molds are commonly found in buildings that have water damage, the study shows the importance of quickly cleaning up water damage and mold in homes.

The researchers studied 289 infants who were part of the Cincinnati Childhood Allergy and Air Pollution Study. They collected house dust samples when the infants were 8 months old and analyzed the samples for 36 molds, endotoxin, house dust mite, cat, dog, and cockroach allergens. The researchers found that 25 percent of children whose parents had allergies were asthmatic by age 7 and that exposure to *Aspergillus ochraceus*, *Aspergillus unguis*, and *Penicillium variable* was linked to asthma development in the high-risk study population.

*Citation:* Reponen T, Lockey J, Bernstein DI, Vesper SJ, Levin L, Khurana Hershey GK, Zheng S, Ryan P, Grinshpun SA, Villareal M, Lemasters G. 2012. Infant origins of childhood asthma associated with specific molds. J Allergy Clin Immunol 130(3):639-644.e5. [Story Related Editorial](#)

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

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## Intramural papers of the month

*By Brant Hamel, Sonika Patial, and Jeffrey Stumpf*

- [Maternal smoking during pregnancy leads to modifications in child's DNA](#)
- [Novel protein limits programmed mutagenesis to antibody-producing genes](#)
- [Cerium dioxide nanoparticles may lead to human immune cell death](#)
- [Study dissects regulation of innate immunity by p53 tumor suppressor](#)

## Maternal smoking during pregnancy leads to modifications in child's DNA

A recent study conducted by NIEHS researchers identified a DNA modification in children born to mothers who smoked during pregnancy. This modification, known as cytosine DNA methylation, has been proposed to be

one of the mechanisms that may lead to a variety of adverse health effects in these children, such as low birth weights, childhood cancers, respiratory illness, obesity, and high blood pressure.

In the present study, researchers determined if maternal smoking during pregnancy could affect cytosine DNA methylation in a child's DNA. The researchers took advantage of the new Infinium HumanMethylation450 Beadchip (450K) technology, which has the capability of identifying DNA methylation at over 470,000 cytosine-guanine dinucleotide (CpG) sites, common markers of DNA methylation, across the genome. They used this platform to measure DNA methylation in 1,062 infant cord blood samples from a birth cohort in Norway.

Researchers identified significantly different methylation for 26 CpGs and mapped them to 10 different genes. The identified genes play a key role in tobacco smoke detoxification and diverse developmental processes. These findings implicate DNA methylation changes as a potential pathogenic mechanism responsible for adverse health outcomes in children from mothers who smoked during pregnancy. **(SP)**

*Citation:* Joubert BR, Håberg SE, Nilsen RM, Wang X, Vollset SE, Murphy SK, Huang Z, Hoyo C, Midttun O, Cupul-Uicab LA, Ueland PM, Wu MC, Nystad W, Bell DA, Peddada SD, London SJ. 2012. 450K epigenome-wide scan identifies differential DNA methylation in newborns related to maternal smoking during pregnancy. *Environ Health Perspect*; doi:10.1289/ehp.1205412 [Online 31 July]. [Story](#)

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## **Novel protein limits programmed mutagenesis to antibody-producing genes**

In the July 25, 2012 edition of the *Journal of Biological Chemistry*, NIEHS researchers reported that the newly characterized SLIP-GC protein protects B lymphocytes genome from the mutagenic actions of activation-induced deaminase (AID) activity. Led by the Somatic Hypermutation Group, the study suggests SLIP-GC may be a key component regulating AID such that it only targets the regions in the DNA that encode highly variable antibodies.

Immune responses produce a myriad of different antibodies to increase the chances of developing antibodies that bind to the infectious agent. Antibody diversification requires drastic changes in the DNA sequence at specific regions of the immunoglobulin genes (Ig). AID is a cytosine deaminase that alters nucleotides and produces DNA breaks, thus randomly altering the genetic code and producing antibodies with different amino acid sequences. Targeting of AID to regions that promote antibody diversity is crucial, as untargeted AID activity could lead to genome instability.

The study used a newly created mouse model deficient in SLIP-GC and showed increases in the types of mutations that are expected from AID activity in both Ig and non-Ig regions. This initial characterization shows the importance of SLIP-GC on limiting untargeted mutagenesis, and future studies will use this model to understand how SLIP-GC negatively regulates AID activity. **(JS)**

*Citation:* Richter K, Burch L, Chao F, Henke D, Jiang C, Daly J, Zhao ML, Kissling G, Diaz M. 2012. Altered pattern of immunoglobulin hypermutation in mice in SLIP-GC. *J Biol Chem*; doi:10.1074/jbc.M112.340661 [Online 25 July 2012].

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# Cerium dioxide nanoparticles may lead to human immune cell death

A new study by NIEHS researchers using human peripheral blood monocytes from healthy donors shows that cerium dioxide (CeO<sub>2</sub>) nanoparticles at environmentally relevant exposure levels causes cell death via apoptosis and autophagy. It is the first report on the effects of CeO<sub>2</sub> nanoparticles in primary human cells and given the fact that CeO<sub>2</sub> emissions from diesel fuel are estimated to reach 22 million pounds per year in Europe, it is vital to understand their potential impact on human health.

Researchers exposed isolated human monocytes to low doses of CeO<sub>2</sub> nanoparticles for 20 to 40 hours. Significant increases in cell death were observed through an apoptotic mechanism that was independent of caspase activation, but dependent on mitochondrial damage and induction of apoptosis-inducing factor. Cell death was also mediated through autophagy, which increased if the p53 tumor suppressor protein was inhibited. Given that monocytes are crucial for human immunity, the work suggests even at low doses CeO<sub>2</sub> nanoparticles may have detrimental effects on human health. Furthermore, the results underscore the need for critical evaluation of environmentally relevant concentrations of other nanomaterials on primary human cells. **(BH)**

*Citation:* Hussain S, Al-Nsour F, Rice AB, Marshburn J, Yingling B, Ji Z, Zink JI, Walker NJ, Garantziotis S. 2012. Cerium dioxide nanoparticles induce apoptosis and autophagy in human peripheral blood monocytes. ACS Nano 6(7):5820-5829.

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# Study dissects regulation of innate immunity by p53 tumor suppressor

NIEHS researchers demonstrated that innate immune responses can be enhanced by DNA damage. They established a chain of events in which the lesions stabilize the p53 tumor suppressor that then increases expression of immune genes. Published in Cancer Research, the paper suggests that induction of the p53 tumor suppressor might provide opportunities to kill tumor cells through the immune response. This important link between p53 and immune response also suggests an exciting possibility of therapeutic vaccination to treat cancer.

The studies, performed by researchers in the Chromosome Stability Group, were based on their previous characterization of the consensus sequence in gene promoters bound by p53 and the identification of Toll-like receptor (TLR) family of innate immunity genes as being likely candidates for p53 regulation. The authors used human cancer cell lines with a variety of p53 mutations to show that a change in p53 function affects its ability to induce some TLR genes.

Both DNA damaging agents and TLR activating ligands are widely used in cancer treatment. Since each of the 10 member TLR gene family tested was induced differently in cell-type and agent-dependent manners, these findings suggest that the matrix of p53 status, chromosome stress and responsiveness of individual TLRs should be considered in cancer diagnosis and in cancer therapeutic strategies that target the TLR pathway. **(JS)**

*Citation:* Shatz M, Menendez D, Resnick MA. 2012. The human TLR innate immune gene family is differentially influenced by DNA stress and p53 status in cancer cells. Cancer Res 72(16):3948-3957.

(Brant Hamel, Ph.D., is an Intramural Research Training Award (IRTA) fellow in the NIEHS Laboratory of Signal Transduction. Sonika Patial, D.V.M., Ph.D., is a visiting fellow in the NIEHS Laboratory of Signal Transduction. Jeffrey Stumpf, Ph.D., is a research fellow in the NIEHS Laboratory of Molecular Genetics.)

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# Inside the Institute

## NIEHS kicks off CFC and boosts pledge goal

By Eddy Ball

The great chili chefs of NIEHS were back on the job Sept. 18, as the Institute kicked off its 2012 [Greater North Carolina Combined Federal Campaign \(CFC\)](#) drive. Working from tables set up in the main building’s lobby, volunteers served up virtually every imaginable iteration of chili as part of a drive to raise \$115,000 in charitable pledges from NIEHS employees, by the conclusion of the campaign Dec. 15.

CFC at NIEHS is part of the world’s largest workplace giving campaign. When Director of the Office of the CFC Keith Willingham, spoke to federal employees as the 2012 drive began in Washington, D.C., Sept. 1, he said, “2011 was not only the 50th anniversary of the creation of the CFC by President John F. Kennedy — it also marked the first time total pledges have exceeded \$7 billion since the inception of the CFC.”

That total included \$113,000 in 2011 pledges by NIEHS employees, part of a total of \$272 million in pledges from almost one million federal employees.



Co-chair Long is located on the second floor of the main building B-module, room 222. (Photo courtesy of Steve McCaw)



**Linked video:**  
[Watch OPM Director John Berry discuss the CFC \(01:43\)](#)

(Launches in new window)

Download Media Player:  Flash [↗](#)

### New leadership for 2012 drive

This year’s coordinators are Office of Management employees [Claire Long](#), a member of Associate Director for Management Joellen Austin’s staff, and [Scott Redman](#), of the Financial Management Branch. Like their predecessors, they will enjoy the enthusiastic support of NIEHS/NTP Director Linda Birnbaum, Ph.D., who opened the cook-off by welcoming employees to the opening of the 2012 campaign and encouraging everyone at NIEHS to participate.

“Even in this tremendously tight economy,” Birnbaum said, “people are really, really understanding that there are those in our community who need help.” She emphasized that pledges, one-time gifts, and even loose change in the CFC jars on campus add up and translate into help for those who need it.



Co-chair Redman also works in the Rall Building, room B213. (Photo courtesy of Steve McCaw)

Birnbaum urged employees to look through the [CFC Charity List](#), with its 2,861 approved charities, ranging from hometown relief organizations, such as the Durham Rescue Mission, to large international efforts. The list supplies information about each charity, including the percentage of revenue it devotes to administrative costs.

### Advantages of giving through CFC

Birnbaum referred to several of the five compelling reasons for making a pledge through CFC, listed by John Berry, director of the Office of Personnel Management (OPM), which oversees the national CFC campaign:

- It offers payment by payroll deduction, which lets employees spread their contributions across the entire year.
- It gives charities a steady source of revenue throughout the year.
- It has low overhead costs, so more money goes to the charity.
- It is convenient for employees, who can pledge online and have documentation for their tax records.
- It shows all Americans that federal employees care about their communities.



*As the rain fell outside, Birnbaum spoke to employees about the need to help neighbors in need at home and abroad. (Photo courtesy of Steve McCaw)*

### Pledging is easy and fun

**Online** — Visit the official website of the [Greater North Carolina Area CFC](#) to pledge, authorize payroll deductions, and find out more about participating charities.

**Contact NIEHS division chairs** — More information about CFC, pledging, and participating charities is available just an email or phone call away by contacting these volunteers:

- [Elizabeth Ruben](#), Division of Extramural Research and Training
- [Bob Petrovich](#), Division of Intramural Research
- [Eli Ney](#) and [Pat Stockton](#), Division of the National Toxicology Program
- [Debbie Wales](#), Office of the Director
- [Dona McNeill](#), Office of Management
- [Leigh Voldness](#), Office of Research Facilities
- [Delise Mahoney](#), Office of Human Resources

**Attend special events** — the CFC will sponsor fundraising events in October and November, including the Charity Fair and Bake Sale on Oct. 2, the Book Sale in C Mall and Keystone Lobby Oct. 23-25, as well as the fun run with employees of the U.S. Environmental Protection Agency (date to be determined).



*Disabled veteran April Cook was on hand to show off her companion service dog, Claire, and encourage pledges to [Paws4Vets](#) (CFC19324), which trained the dog and presented it to her free of charge. Cook served four tours in Iraq and Afghanistan, and she credits Claire with helping her cope with war-related anxiety and other effects of post-traumatic stress. (Photo courtesy of Steve McCaw)*



The event featured plenty of chili and drew a stream of hungry people eager to sample it. Serving at this end of the table were, left to right, CFC representative Rob Roy, along with NIEHS employees Bill Quattlebaum and Long. (Photo courtesy of Steve McCaw)



The NIEHS band was on hand to provide background music. Horn players, from left to right, Dick Sloane, Roger Callahan, and Miranda Bernhardt entertained employees at the kick-off event. (Photo courtesy of Steve McCaw)

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# Feds Feed Families drive underscores NIEHS generosity

*By Eddy Ball*

NIEHS staff donated 3,600 pounds of food and toiletries during the 2012 Feds Feeds Families campaign, beating its 2011 performance and its 2012 goal. Of that total, nearly 250 pounds was donated directly by members of the American Federation of Government Employees (AFGE) Local 2923, which co-sponsored the drive along with NIEHS and the Research Triangle Chapter of Blacks In Government (BIG).

The food, toiletries, infant care products, and household cleaning items were donated to the Durham Rescue Mission and the Food Bank of Central and Eastern North Carolina.

In a message to employees following the close of the drive Aug. 31, NIEHS/NTP Director Linda Birnbaum, Ph.D., specifically acknowledged her gratitude for the leadership of the 2012 co-chairs — Monya Brace (NIEHS), Bill Jirles (AFGE), and Annette Rice (BIG).



The team of coordinators, from left to right, included Brace, Rice, and Jirles, who could be proud of a record-breaking drive again this year. (Photo courtesy of Steve McCaw)

“In beating our own goal, as well as our totals from last year, we joined a successful NIH-wide effort, which collected a total of 17,791 pounds,” Birnbaum wrote. “I am sure you share my pride in the generosity of our NIEHS family and that of our larger NIH community.”

By donating approximately one-fifth of the NIH total, NIEHS made a disproportionately large contribution to helping boost food supplies at charitable organizations. NIEHS is one of 27 NIH institutes and centers (ICs) and has a workforce that falls about mid-range in comparison to its sister ICs.

“I’m not surprised that we’re top performers,” said NIEHS Deputy Associate Director for Management Chris Long. “NIEHS is fortunate to have incredibly generous employees with a strong commitment to their communities.”



Volunteers staffed collection stations at Keystone, above, and on the main NIEHS campus. (Photo courtesy of Steve McCaw)



The food and other items piled up at collection sites, such as this one in Keystone. (Photo courtesy of Steve McCaw)



Volunteers loaded their personal cars for the trip to north Raleigh Aug. 31. (Photo courtesy of Steve McCaw)

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## NIEHS honors dedication and longevity

By Eddy Ball

Continuing a long-standing tradition, NIEHS honored employees for their decades of service during a Sept. 13 ceremony. As in previous years, employees enjoyed refreshments served by members of the NIEHS leadership, in a reception following the presentation of plaques in Rodbell Auditorium.

Director Linda Birnbaum, Ph.D., spoke briefly, before turning over the podium to Associate Director for Management Joellen Austin. “I think there’s a certain idealism for those of us who work in the government and stay in the government,” Birnbaum told the audience. “We like being responsible to the taxpayer and the American public. ... We’re really here to recognize those of us who have logged a lot of time in federal service.”

Birnbaum, herself a 33-year veteran of federal service, noted that NIEHS was recognizing a collective total of 1,100 years of service with the awards. “When we work for the government, we know we’re really working for the American people,” she said.

Appropriately enough for a celebration of dedication and longevity, the presentation of awards began and ended with the recognition of NTP geneticist Jack Bishop, Ph.D. Bishop was the sole retiree in attendance and one of three 40-year veterans in attendance.

In 2009, Birnbaum began a new tradition by establishing a separate ceremony specifically to honor longevity of service.



*A beaming Bishop, left, received his retirement plaque from Birnbaum. (Photo courtesy of Steve McCaw)*



*Madhumita Ray was recognized for 10 years of federal service. Ray is a biologist with the Laboratory of Molecular Genetics. (Photo courtesy of Steve McCaw)*

## Awardees

### 10 Years

Judy Bartz  
Marilyn Diaz  
Sally Eckert-Tilotta  
Paul Foster  
Dagoberto Grenet  
Michael Humble  
Anna Jansen  
Melissa Jones  
Steven Kleeberger  
Elizabeth McNair  
Theodore Outwater  
Madhumita Ray  
Manas Ray  
Troy Simpson  
Jason Stanko  
Marva Wood

### 20 Years

Lisa Edwards  
Susan Hart  
Denise Lasko  
Beth Ragan  
Yvette Rebollosa  
Dudley Riner  
Tonya Stonham  
Tatsuya Sueyoshi  
Gregory Travlos  
Carol Trempus  
David Umbach  
Richard Weaver  
Belinda Wilson

### 30 Years

Lois Annab  
Alma Britton  
Alan Clark  
Debra Del Corral  
Rachel Frawley

Harvey Gates  
Margaret George  
Cynthia Innes  
Thomas Kunkel  
Patricia Lamb  
Christopher Lee  
James McDonough  
Connie Riley  
Margarita Roque  
Valeria Shropshire  
James Westmoreland

### 40 Years

Jack Bishop  
Vickie Englebright  
Jennie Foushee  
Eugenia Goulding  
Sharon Soward

### Retired

Jack Bishop  
Po Chuen Chan  
Joyce Daye  
Gregg Dinse  
John Drake  
Franklin Johnson  
Elizabeth Kennington  
Jo Ann Lewis  
James Mason  
Mary Myers  
Judy Palmer  
Lee Pedersen  
John Peterson  
Sharyn Rigsbee  
Joseph Roycroft  
Michael Shelby  
Julius Thigpen  
Kenneth Tomer



*Recognized for 20 years of service, Dudley Riner is a member of the Financial Management Branch. (Photo courtesy of Steve McCaw)*



*Health and Safety Branch team member VeeVee Shropshire showed off her winning smile, as she received the plaque honoring her 30 years of government service. (Photo courtesy of Steve McCaw)*



*Vickie Englebright was one of just five employees celebrating their 40th year of service. (Photo courtesy of Steve McCaw)*



*Members of leadership turned out to show their appreciation for dedication and longevity, by working the refreshment serving line. NTP Associate Director John Bucher, Ph.D., left, and Division of Extramural Research and Training Director Gwen Collman, Ph.D., poured punch, as Rob Levine, right, filled his plate. (Photo courtesy of Steve McCaw)*



*This group of awardees represented a combined total of 130 years of service. Shown, left to right, are Margaret George, Lois Annab, Shropshire, Alma Britton, and Dagoberto Grenet. (Photo courtesy of Steve McCaw)*

*Along with his plaque, 10-year veteran Troy Simpson, left, received best wishes from colleague Dona McNeill. (Photo courtesy of Steve McCaw)*

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