

April 2011

## NIEHS Spotlight



### [NIEHS wants visionary ideas for strategic planning](#) Video

NIEHS is seeking input for its new strategic plan. There are two ways for people to get involved now, by submitting a visionary idea and nominating a workshop participant.



### [NIH launches largest oil spill health study](#)

The GuLF STUDY (Gulf Long-term Follow-up Study) will follow 55,000 cleanup workers and volunteers in four states affected by the oil spill for up to 10 years.



### [Shaping protocol for the GuLF STUDY](#)

Two weeks after launching the historic GuLF STUDY (Gulf Long-Term Follow-up Study), NIH study leaders met with advisory groups March 14-16 for input on their protocol.



### [50th SOT meeting breaks record](#) Audio

The yearlong anticipation of the 50th annual meeting of the Society of Toxicology (SOT) came to a successful culmination March 6-10 with a record-setting 8,000 attendees.



### [Dedication of new Tox21 robot system to test 10,000 chemicals for toxicity](#) Video

Key players involved in the Tox21 effort gathered March 10 at the NIH Chemical Genomics Center to dedicate a new high-speed robot screening system.

## Science Notebook



### [NIEHS scientists join forces with green chemists](#)

The scientists worked toward development of a consensus statement and green testing protocols for bringing a next generation of safer chemicals into the marketplace.



### [Fry outlines a systems level approach to understanding arsenic](#)

During a seminar at Duke University Feb. 25, NIEHS grantee Rebecca Fry, Ph.D., explored this chemical as a medicine and as a poison.



### [Microglia: A complex resident immune cell of the brain](#)

NIEHS Principal Investigator Jean Harry, Ph.D., introduced the complex processes of neuroinflammation in the brain during a talk March 4 at Duke University.



### [Trainees honored for scholarship and service by SOT](#)

Four NIEHS/NTP trainees returned home from the 50th anniversary meeting of the Society of Toxicology with honors for their exceptional scholarship and service.



### [Research fellow shines at drug development meeting](#)

Xueqian (Shirley) Wang, Ph.D., received a first-place prize for her poster presentation at the RTP Drug Metabolism Discussion Group Winter Symposium March 17.

## NIEHS Spotlight



### [Postdoctoral trainee launches career in health care communications](#)

Sophie Bolick, Ph.D., left NIEHS recently for a position at MedThink Communications, a health care communications company in Raleigh, N.C.



### [NIMH director reaches out to NIEHS](#)

Director of the National Institute of Mental Health Thomas Insel, M.D., explored the topic of “Why NIMH Cares About NIEHS” during a presentation here March 1.



### [Environmental stewards hold annual meeting at NIEHS](#)

Continuing a five-year tradition, NIEHS hosted the North Carolina Environmental Stewardship Initiative annual meeting March 11 in Robell Auditorium.



### [University of Washington trainee headed to Lindau](#) ▶ Video

University of Washington trainee Judit Marsillach Lopez, Ph.D., will attend the prestigious Lindau Nobel Laureate Meeting June 26-July 1 in Germany.



### [Young NIEHS fellow featured in new video](#) ▶ Video

As she pursues her dream of becoming a doctor, trainee Quiana Childress stars in a new video produced by her sorority to help raise funds for scholarships.

## Science Notebook



### [NIEHS investigators find link between DNA damage and immune response](#)

NIEHS researchers offer the first evidence that DNA damage can lead to the regulation of inflammatory responses, the body's reaction to injury.



### [Jetten to investigate a novel stem cell treatment for diabetes](#)

NIH announced on Feb. 25 supplemental support of \$86,000 in fiscal year 2011 for an innovative research project headed by NIEHS cell biologist Anton Jetten, Ph.D.



### [Pollution leads to rapid evolution in some fish species](#) ▶ Audio

New NIEHS-funded Superfund research finds a population of Atlantic tomcod (*Microgadus tomcod*) in the Hudson River has rapidly evolved resistance to PCBs.



### [Infertility linked to PCB exposure](#)

NIH-funded investigators report that PCBs, in concentrations representative among the general U.S. population, were associated with failed embryo implantations.



### [New hope in the treatment of cystic fibrosis](#)

NIEHS-funded scientists recently unveiled the discovery of a potential therapeutic that could dramatically transform the treatment of lung diseases.

## NIEHS Spotlight



### [NIEHS participants at upcoming NAS workshop on the microbiome](#)

NIEHS is playing a major role as sponsor and participant in the upcoming workshop on “Interplay of the Microbiome, Environmental Stressors, and Human Health,” April 27-28.



### [Mark your calendars for the NIEHS career fair](#)

The 14th annual NIEHS Biomedical Career Fair will be held April 29 at the U.S. Environmental Protection Agency conference center in Research Triangle Park, N.C.

## Inside the Institute



### [Black History Month forum focuses on mental health](#)

The RTP Chapter of Blacks In Government and the NIEHS Diversity Council sponsored a program Feb. 23 on health issues in the African-American community.



### [NIEHS helps teachers learn how to teach science more effectively](#)

Teachers from across North Carolina gathered in Rodbell Auditorium Feb. 28 to draw on the resources of NIEHS to liven up their science lessons.

## Science Notebook



### [Thomas explores advances in risk assessment using genomics](#)

Toxicologist Russell Thomas, Ph.D., a genomics specialist at The Hamner, spoke at NIEHS March 21 on the application of non-traditional approaches to risk assessment.



### [Agreement increases international cooperation to reduce animal testing](#)

Korea joined partners in the U.S., E.U., Canada, and Japan, as representatives signed an historic Memorandum of Cooperation in Washington, D.C., March 8.



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

The April issue of EHP takes a look at a new trend in public health preparedness in its feature article, “Preparing a People: Climate Change in Public Health.”



### [Upcoming distinguished lecturer Ron de Kloet](#)

The NIEHS Distinguished Lecture Series continues a series of talks on neuroscience when it hosts a lecture by neuroendocrinologist Ron de Kloet, Ph.D., April 12.



### [Upcoming distinguished lecturer Edison Liu](#)

The Distinguished Lecture Series shifts gears on April 22 when it hosts geneticist Edison Liu, M.D., for a talk on “Systems Biology in Cancer Medicine: Harnessing Complexity.”

## Calendar of Upcoming Events

- **April 5**, in Rodbell Auditorium, 8:30 a.m.-5:00 p.m. — NTP Technical Reports Peer Review Meeting
- **April 5-6 (offsite event)**, at the Pew Charitable Trusts in Washington, D.C., 8:30 a.m.-5:00 p.m. — Workshop on Enhancing the Food and Drug Administration's Evaluation of Science to Ensure Chemicals Added to Human Food Are Safe
- **April 7**, in Keystone 1003AB, 10:00-11:00 a.m. — Keystone Science Lecture Seminar Series with Olivier Deschenes, Ph.D., topic TBA
- **April 11**, in Rodbell Auditorium, 11:30 a.m.-12:30 p.m. — Yikang Rong, Ph.D., discussing "Sequence-independent telomere maintenance in *Drosophila*," as part of the Laboratory of Molecular Genetics Fellows Invited Guest Lectures Series
- **April 11**, in Rodbell Auditorium, 1:30-2:30 p.m. — Seminar on "A New NHGRI/NIH Strategic Plan: Charting a Course for Genomic Medicine" by Eric Green, M.D., Ph.D.
- **April 12**, in Rodbell Auditorium, 11:00 a.m.-12:30 p.m. — Distinguished Lecture by Ron de Kloet, Ph.D., on "Resilience or vulnerability to environmental challenge? A question of stress, genes, and balance"
- **April 13**, in Rodbell Auditorium, 8:30 a.m.-5:30 p.m. — NTP Board of Scientific Counselors Meeting
- **April 14-15**, in Rodbell Auditorium, 8:30 a.m.-5:30 p.m. — GEI Exposure Biology Grantee Meeting
- **April 22**, in Rodbell Auditorium, 11:00 a.m.-12:30 p.m. — Distinguished Lecture by Edison Liu, M.D., "Systems Biology in Cancer Medicine: Harnessing Complexity"
- **April 25**, in Rodbell Auditorium, 11:30 a.m.-12:30 p.m. — Presentation by Jodi Nunnari, Ph.D., title TBA, as part of the Laboratory of Molecular Genetics Fellows Invited Guest Lectures Series
- **April 27**, in Rodbell Auditorium, 9:00 a.m.-4:00 p.m. — Symposium on Sirtuins in Aging and Age-associated Diseases
- **April 27-28 (offsite event)**, at the 20 F Street Conference Center in Washington, D.C. — Emerging Science for Environmental Health Decisions workshop, "Interplay of the Microbiome, Environmental Stressors, and Human Health," [register](#)
- **April 29 (offsite event)**, at the U.S. Environmental Protection Agency conference center in Research Triangle Park, N.C., 8:30 a.m.-5:00 p.m. — 14th Annual NIEHS Biomedical Career Fair
- View More Events: [NIEHS Public Calendar](#)

## Extramural Research

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

- [Resveratrol protects mother and fetus from immunotoxic effects of TCDD](#)
- [Human-induced pluripotent stem cells exhibit extensive epigenomic reprogramming](#)
- [Arsenic exposure may increase mortality from tuberculosis](#)
- [Tobacco smoke enhances the progression of diabetic nephropathy](#)

## Intramural Research

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

- [SNPs modulate cellular stress response](#)
- [Decreasing DNA binding may reverse mutator phenotype](#)
- [Regulation of metabolic syndrome by the nuclear receptor TAK1/TR4](#)
- [Occupational hazards of agriculture](#)

# NIEHS Spotlight

## NIEHS wants visionary ideas for strategic planning

By Ernie Hood

The National Institute of Environmental Health Sciences (NIEHS) is seeking input for its new strategic plan. There are two ways for people to get involved now. They can submit a visionary idea, and nominate a workshop participant.

“We are looking for innovative ideas to help define the Institute’s future directions, research goals, and resource priorities,” said NIEHS Deputy Director Richard Woychik, Ph.D., who is leading the strategic planning effort.

Visionary ideas can be submitted through a user-friendly Web site at <http://strategicplan.niehs.nih.gov/>. All submitted ideas will be posted to the Web site, and anyone can comment on the ideas or give a thumbs-up or thumbs-down rating. The Web site also integrates with Facebook and Twitter. Submissions will be accepted through April 30.

NIEHS is also accepting nominations for a stakeholder community workshop that will be held in mid-July in Research Triangle Park, N.C. You can nominate yourself, a respected colleague or anyone who is passionate about understanding our environment for the purpose of improving public health and preventing disease. Nominations can be made at <http://www.niehs.nih.gov/about/od/strategicplan/nomination/index.cfm>.

### Anyone can be a part of the process

The 15-month process of formulating a new five-year strategic plan for NIEHS officially got underway March 1 in an all-hands meeting at the Institute. NIEHS/NTP Director Linda Birnbaum, Ph.D., emphasized the importance of gaining input from everyone with an interest in NIEHS and environmental health.



Woychik is spearheading the Institute’s 2012-2016 Strategic Planning process. (Photo courtesy of Steve McCaw)



The March 1 launch of the NIEHS Strategic Planning process drew a capacity audience to Rodbell Auditorium. (Photo courtesy of Steve McCaw)

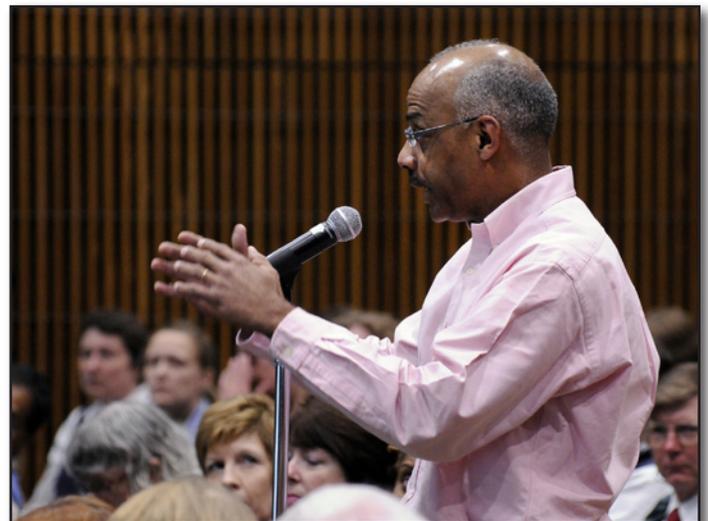
“Our goal is to bring together all of your wisdom to answer the challenges, to help determine our priorities, and to make sure that we are doing everything possible to fulfill our mission as a critical part not only of NIH, but of the Department of Health and Human Services, and the whole nationwide enterprise in environmental health sciences,” Birnbaum said in her opening remarks.

In his presentation, Woychik described the process itself in more detail, including the time line of events that will lead to the publication of the final plan in June 2012. He urged everyone present to get involved. “The process is really all about engaging all of you, both internal to NIEHS and the external community,” he said. “We really want to hear from you, and the input that you provide... will be heard and will be part of the deliberation to come up with our new mission, vision, strategic goals, and strategies.”

After presenting the timeline information, Woychik introduced Sheila Newton, Ph.D., director of the Office of Planning, Policy, and Evaluation, who outlined the online access points for people to provide their input to the strategic planning process. Those resources include the main strategic plan [Web site](#), which also can be accessed via a prominent link on the [NIEHS home page](#).



*Newton took the audience through the process of using social voting and ideation software to enter visionary ideas and vote online. (Photo courtesy of Steve McCaw)*



*NTP Chief of Cellular and Molecular Pathology Robert Sills, D.V.M., Ph.D., asked how the ideas of non-scientific personnel would be accommodated in the strategic planning process. (Photo courtesy of Steve McCaw)*

A screenshot of a video player interface. On the left is a video player with a play button. To the right of the player is a text box with the following content:

**Linked video:**  
[Watch Newton demonstrate how to use the interactive web portals now online to provide input to the Strategic Planning process \(09:58\)](#)  
(Launches in new window)

At the bottom of the player area, it says "Download Media Player: Quicktime".

The site details the anticipated timeline and offers direct links to the two major processes currently available for both internal and external interested parties to provide their input. First, there is an interactive site called [Visionary Ideas](#), where people can post their big-picture ideas about the strategic plan, and can vote to agree, disagree, and/or comment on ideas posted by others. Also, there is a link to a page where people can [nominate](#) themselves or others to be invited to attend the intensive 2-3-day Community Workshop planned for July 2011.

The public will have many opportunities to provide input and review throughout the strategic planning process. Visit <http://www.niehs.nih.gov/strategicplan/> for more information about the process and the timeline for establishing the new NIEHS strategic plan, or to review the existing 2005-2011 strategic plan.

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



NIEHS Principal Investigators Ken Korach, Ph.D., left, and Mitch Eddy, Ph.D., center, were among people from across the Institute who turned out to learn more about the planning process. (Photo courtesy of Steve McCaw)



Birnbaum, right, and Program Analyst Kimberly Thigpen Tart, J.D., enjoyed a lighter moment during the all-hands Strategic Planning meeting. (Photo courtesy of Steve McCaw)

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# NIH launches largest oil spill health study

By Christine Flowers

A new study that will look at possible health effects of the Gulf of Mexico’s Deepwater Horizon oil spill on 55,000 cleanup workers and volunteers began Feb. 28 in towns across Louisiana, Mississippi, Alabama, and Florida.

The [GuLF STUDY \(Gulf Long-term Follow-up Study\)](#) is the largest health study of its kind ever conducted among cleanup workers and volunteers, and is one component of a comprehensive federal response to the Deepwater Horizon oil spill. The study is being conducted by NIEHS and is expected to last up to 10 years. Many agencies, researchers, and outside experts, as well as members of local communities, have provided input into how the study should be designed and implemented.

“Over the last 50 years, there have been 40 known oil spills around the world. Only eight of these spills have been studied for human health effects,” said [Dale Sandler, Ph.D.](#), chief of the Epidemiology Branch at NIEHS and principal investigator of the GuLF STUDY. “The goal of the GuLF STUDY is to help us learn if oil spills and exposure to crude oil and dispersants affect physical and mental health.”



GuLF STUDY Principal Investigator Dale Sandler (Photo courtesy of Steve McCaw)

Over time, the GuLF STUDY will generate important data that may help inform policy decisions on health care and health services in the region. Findings may also influence responses to other oil spills in the future.

“We are enrolling workers and volunteers because they were closest to the disaster and had the highest potential for being exposed to oil and dispersants,” said Sandler.

The GuLF STUDY will reach out to some of the 100,000 people who took the cleanup worker safety training and to others who were involved in some aspect of the oil spill cleanup. The goal is to enroll 55,000 people in the study. Individuals may be eligible for the study if they satisfy the following criteria:

- Are at least 21 years old
- Did oil spill cleanup work for at least 1 day
- Were not directly involved in oil spill cleanup, but supported the cleanup effort in some way or completed oil spill worker training

Working from lists of people who trained or worked in some aspect of the oil spill response, the GuLF STUDY will contact potential participants by mail, inviting them to take part in the study.

The study was developed to make participation as easy and convenient as possible (see text box). In addition, the GuLF STUDY incorporates safeguards to protect the privacy and confidentiality of personal information.

NIH is funding the GuLF STUDY. A small part of the funds have been provided by BP to NIH specifically for research on the health of Gulf-area communities following the spill, although BP is not involved in the study.

For more information, call the GuLF STUDY toll-free number at 1-855-NIH-GULF (1-855-644-4853) or visit the GuLF STUDY Web site at <http://www.niehs.nih.gov/GuLFSTUDY>.



*In December 2010, NIEHS/NTP Director Linda Birnbaum, Ph.D., honored the Institute's Gulf oil spill response team. Shown, back row, from left to right, Ted Outwater, Vanessa Knight, Emily Starnes, Kathy Ahlmark, Sharon Beard, Joseph "Chip" Hughes, Steve Kleeberger, John Bucher, Gwen Collman, Scott Masten, Kent Stone, Darryl Zeldin, Paul Jung, and James Remington. Seated, from left to right, Cheryl Thompson, Christine Flowers, Dale Sandler, Laurie Johnson, Richard Kwok, and Carolyn Mason. Not pictured: Aaron Blair, Allen Dearry, Larry Engel, Lindsay Lloyd, Robin Mackar, Aubrey Miller, Connie Riley, Dudley Riner, Margarita Roque, Angie Sanders, William A. Suk, and Claudia Thompson. (Photo courtesy of Steve McCaw)*

## Being a part of the historic GuLF STUDY

All participants will be asked to complete an initial telephone interview, and provide updated contact information once a year. During the telephone interview, participants will be asked questions about the work they did with the oil spill cleanup, and about their health, lifestyle, and job history.

About 20,000 participants will be invited to take part in the second phase of the study, which involves a home visit and follow-up telephone interviews in subsequent years. Small samples of blood, urine, toenail clippings, hair, and house dust will be collected during the home visit, and clinical measurements such as blood pressure, height and weight, urine glucose, and lung function will be taken.

If at any time in the course of the study, the need for mental or medical health care is evident, participants will be given information on available healthcare providers or referred for care. The study leaders have up-to-date information on healthcare providers and a medical referral process in place as part of the study. Materials will be available in English, Spanish, and Vietnamese.

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## Shaping protocol for the GuLF STUDY

*By Eddy Ball*

Two weeks after launching the historic [GuLF STUDY \(Gulf Long-Term Follow-up Study\)](#), NIH study leaders met with advisory groups March 14-16 for input on their protocol. The meetings involved a full day of presentations before the GuLF STUDY Scientific Advisory Board (SAB), followed by two days of presentations by exposure assessment consultants and members of the GuLF STUDY Exposure Assessment Working Group (EAWG).

The meetings opened with comments to SAB members from NIEHS Deputy Director Richard Woychik, Ph.D., and James Anderson, M.D., Ph.D., director of the NIH Division of Program Coordination, Planning, and Strategic Initiatives.

### The spill that dwarfed them all

Standing in for NIEHS/NTP Director Linda Birnbaum, Ph.D., Woychik welcomed SAB members to NIEHS, underscored the enormity of the spill and its largely unknown effects on health, and praised the timeliness of the NIEHS response. “This is record time,” he said of the study, which evolved from a two-page memorandum written by Principal Investigator Dale Sandler, Ph.D., in June 2010.

Over the intervening ten months, [NIH study leaders](#) ushered their plans through an Institute of Medicine review, held a series of



*Anderson quoted a Science magazine editorial about the study. “The GuLF STUDY will help inform the development of off-the-shelf protocols that will facilitate a response to future spills, [and] it’s already led to a very high level of interagency interactions in the government to consider how to better respond.” (Photo courtesy of Steve McCaw)*

outreach webinars and community advisory meetings, and gained approvals from the study's Institutional Review Board and the Office of Management and Budget.

Anderson, who was representing NIH Director Francis Collins, M.D., Ph.D., stressed the potential of the GuLF STUDY to offer guidance for future emergencies. "This is an historic study," he explained. "It will serve as a model for how to rapidly organize research responses to national disasters." Anderson encouraged SAB members to monitor the transparency and pace of the study as it progresses, as well as the quality of the science involved.

### Public perception is key

Sandler led off the SAB presentations with an update on the study and outline of the cohorts involved. From the estimated 100,000 to 150,000 cleanup and support workers in Louisiana, Mississippi, Alabama, and Florida exposed to oil, dispersants, and other chemicals, the study aims to screen about 86,000 adults and enroll approximately 55,000 for a telephone survey. From that group, a stratified random sample of some 20,000 will become part of an active subcohort receiving home visits and sample collection, with approximately 5,000 identified for more extensive sampling as part of a biomedical surveillance subcohort.

In their presentations, study team members pointed to the central issues of trust and expectation among people in affected areas and the steps the team has taken to boost recruitment and cooperation with the study. "We have to do this study in the daylight," Sandler said of efforts to engage the community and plans to share as much information as possible, as quickly as possible, while also dispelling misinformation that has already taken root in affected communities.

In his presentation on medical referrals, NIEHS Senior Medical Advisor Aubrey Miller, M.D., described strategies and resources for helping home visit agents make primary and secondary care referrals, as they come across people who need treatment for physical and mental disorders.

### Tackling the unknowns

Time and again, over the three days of meetings, participants confronted how much about the oil spill and its effects remains unclear. Study leaders explained that there was no centralized management of the contractors and subcontractors who employed the cleanup and support workers. Even something as basic as identifying prospective subjects involved merging lists from different sources.

As NIEHS Staff Scientist and co-investigator Richard Kwok, Ph.D., observed during the EAWG meeting, "There was a lot of variability, even across the same job," making it difficult to predict how extensively workers were exposed. Use of protective clothing and equipment also varied from site to site and among individuals.



*Kwok, left, and Sandler gave updates on the study and fielded questions from the scientific advisors. They also received praise for how effectively they've taken on the enormous challenges of the study. (Photo courtesy of Steve McCaw)*



*SRA International consultant David Brown reviewed community engagement activities and emphasized, "Outreach will be crucial to the success of this study." (Photo courtesy of Steve McCaw)*



Consultants Patricia Stewart, Ph.D., of Stewart Exposure Assessments, LLC, left, and Mark Stenzel, of Exposure Assessment Applications, LLC, were co-authors of the strategy for exposure assessment and presenters at the meetings. (Photo courtesy of Steve McCaw)



SAB member Lora Fleming, M.D., Ph.D., said that exposure assessment could be confounded if storms and floods disturb oil and dispersants again. “There may be future exposures,” she warned. (Photo courtesy of Steve McCaw)



The one non-scientist on the SAB, Captain Bob Zales, offered a frontline perspective on the stress and uncertainty people faced during the spill and afterwards, as well as the impact of the disaster on mental health in the region. (Photo courtesy of Steve McCaw)

As meticulously as the team has worked to design a comprehensive protocol, Sandler conceded that realities in the field might mean fine-tuning the study design as new challenges and new information surface.

### GuLF STUDY objectives

- Assess health effects associated with oil spill cleanup following the Deepwater Horizon disaster, April 20, 2010
- Investigate biomarkers of adverse biological effects
- Create a resource for future collaborative research

### Health outcomes of interest

- Primary endpoints — respiratory, genotoxic, hematologic, neurologic, immunologic, mental health
- Secondary endpoints — cancer, cardiovascular, hepatic, renal, other

### Proposed timeline

- Feb. 28, 2011 — Begin sending out 2,000 letters to workers in four states to recruit a “vanguard” cohort for a mini-pilot test of protocols and approaches
- March 24, 2011 — Begin telephone interviews of vanguard with home visits beginning May 2, 2011
- April 25-29, 2011 — Open to full cohort, with enrollment and baseline data collection expected to take 18 to 24 months

### Advisory groups

- Community Advisory Group — representatives of state and local government, non-profits, and business interests affected by the spill
- Scientific Advisory Board — addressing scientific issues, priorities, add-on studies, and cost-containment measures
- Exposure Assessment Working Group — addressing the approach, exposure characterization, available data, and anticipated methodology
- Institute of Medicine (IOM) — reviewed the initial plans for the study and will monitor study progress

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# 50th SOT meeting breaks record

By Ed Kang

The yearlong anticipation of the [50th annual meeting](#) of the Society of Toxicology (SOT) came to a successful culmination March 6-10 as a record-setting 8,000 attendees flooded the Washington, D.C., Convention Center. Federal representatives, including NIEHS and NTP scientists, led the way, headlining plenary sessions and leading key science discussions.

“The science of toxicology continues to make its mark on public health,” said Linda Birnbaum, Ph.D., NIEHS/NTP director. “SOT remains an essential venue for the Institute, as together we share a prominent role in advancing the field.”

Birnbaum, a past president of SOT, drew a standing room-only crowd at her “Meet the Director” session, which was both reflective and prognostic. In addition to communicating the Institute’s research highlights for the past year, Birnbaum utilized the forum to unveil — for the first time publicly — the Institute’s strategic planning process. Her discussion sparked interest in developing the vision for the Institute that will encompass the next five years, a theme of keen interest for SOT membership.

## Live updates captivate Twitterverse

For the second year running, more than a dozen NIEHS and NTP staff documented their conference activities by providing live updates from the meeting. Their reports spanned scientific sessions, social activities, meetings with colleagues, and overviews of roundtables and other discussions.

“The excitement of this special event can only be experienced by being there in-person,” said one of the participants in the live updating effort, Paul Jung, M.D., NIEHS chief of staff. “But for those who couldn’t make it to the meeting, these updates are the next best thing.”

More than 70 updates from the 50th annual conference are archived for public viewing on the NIEHS Web site at [www.niehs.nih.gov/LiveatSOT](http://www.niehs.nih.gov/LiveatSOT) and on Twitter ([www.twitter.com/niehs](http://www.twitter.com/niehs)).

## ‘Benchmarks’ poster proves popular

Another success of the conference was the unveiling of the poster titled “Benchmarks in Toxicology” — a joint effort of NIEHS/NTP, the journal *Environmental Health Perspectives*, and SOT. The [poster](#), which describes the people, innovations, discoveries, and events that



*For Birnbaum, the annual SOT meeting has long been a special time. She is the first toxicologist to serve as director of NIEHS/NTP. (Photo courtesy of Steve McCaw)*



*Germa Molec also serves as the project officer for the NTP’s contractual efforts to validate test methods and to assess the potential for chemicals to modulate immune responses in rodent models and is the coordinator of an interagency agreement with the National Institute for Occupational Safety and Health. (Photo courtesy of Steve McCaw)*

have been milestones in the development of the field of toxicology, was a huge attraction at the conference.

A March Environmental Health Perspectives podcast featured an interview about the poster with Peter Goering, Ph.D., SOT secretary and a toxicologist with the U.S. Food and Drug Administration. Goering was one of six distinguished panel members who evaluated more than 200 nominations submitted from SOT members for consideration in the poster.



[Listen as Goering discusses how he and other members of the evaluation group chose the people and events that best illustrate the promise and achievements of toxicology \(07:00\)](#)



[Read Transcript](#)

### Scientists honored by SOT

SOT elected former NIEHS trainee and toxicologist Lois Lehman-McKeeman, Ph.D., to serve as vice president-elect on the SOT Council for one year beginning May 1, followed by one year as vice president, one year as president, and one year as past president. NTP biologist [Dori Germolec, Ph.D.](#), was named SOT Councilor for 2011 – 2013, joining her NTP colleague, toxicologist Michael Waalkes, Ph.D., who was elected to the SOT Council last year. Four NIEHS/NTP trainees were honored by SOT specialty sections ([see story](#)).

Lehman-McKeeman is currently a Distinguished Research Fellow in Discovery Toxicology at the Bristol-Myers Squibb Company in Princeton, N.J. She received her Ph.D. from the University of Kansas Medical Center, where she trained with NIEHS [grantee](#) Curtis Klaassen, Ph.D. The recipient of numerous honors, Lehman-McKeeman was employed in the Human and Environmental Safety Division of the Procter and Gamble Company for 15 years prior to joining Bristol-Myers Squibb in 2001.

Germolec served as the group leader of the Environmental Immunology Laboratory within the Laboratory of Molecular Toxicology at NIEHS from 1995 to 2005. She is currently the immunology discipline leader for the NTP and the lead toxicologist for NTP studies on the toxicity of resveratrol and mold exposures. Germolec has published over 100 papers in various areas of toxicology. Her honors include an NIH Merit Award and SOT Best Publication Award in 1995, as well as the Outstanding Young Investigator Award from the Immunotoxicology Specialty Section of the SOT in 2004.

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

## Coming up: APHA Environment Section to celebrate milestone in 2011

The American Public Health Association (APHA) Environment Section is marking its centennial this fall. Anniversary committee co-chair, Allen Dearry, Ph.D., of NIEHS is helping to organize section members and other interested parties to develop a commemorative program. Among the undertakings are a 100-year chronology of the “heroes and milestones” in environmental health, as well as a video and web resource describing the story of environmental public health over the past century.

This year’s meeting of APHA will take place Oct. 29-Nov. 2 in Washington, D.C., with a theme of “Healthy Communities Promote Healthy Minds and Bodies.”

**BENCHMARKS in TOXICOLOGY**

**People** *Contributors to the field of toxicology*

**Federal Government Efforts** *Protecting the nation's health*

**Risk Assessment** *Using toxicology to reduce harm*

**Mechanisms & Metabolism** *Improving our understanding of biological processes*

**1500 Pure Food and Drug Act** The first federal law regulating the marketing of drugs and the first federal food and drug law, which required accurate labeling of drugs and cosmetics. Prior to this, many drugs were sold without any labeling at all.

**1938 Federal Food, Drug, and Cosmetic (FDSC) Act** The first federal law requiring that drugs be safe and effective before they can be marketed. It also required that drugs be labeled with their true identity and that they be tested for safety and efficacy before they can be marketed.

**1972 Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)** FIFRA provided for federal registration, distribution, and use of pesticides to protect human health and the environment. It also provided for the registration of pesticides and the control of their use.

**1970s Lead reduction efforts** Through the Clean Air Act, the Federal Lead Reduction Act, and other efforts, the federal government has made significant progress in reducing lead in the environment. This has been achieved through the regulation of lead in gasoline, lead in paint, and lead in solder.

**1970s Toxic Substances Control Act (TSCA)** TSCA was the first federal law that required the manufacturer or importer of a chemical to provide information about the chemical to the federal government. This information is used to assess the potential risks of the chemical to human health and the environment.

**1974 National Toxicology Program** NTP was established to coordinate and conduct research on the potential risks of chemicals to human health. It is a multi-agency effort involving the EPA, FDA, and other federal agencies.

**1976 Good laboratory practices (GLP)** GLP is a set of principles and procedures that are used to ensure the quality and integrity of data used in the development of a new drug or chemical. It is a requirement for all pharmaceutical and chemical manufacturers.

**1980 Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA)** CERCLA is a federal law that provides for the cleanup of hazardous waste sites. It also provides for the compensation of individuals who are injured by hazardous waste.

**1980 Toxicology testing in the 21st century (Tox21)** Tox21 is a multi-agency effort to develop new methods for testing chemicals for toxicity. It is a collaborative effort between the EPA, FDA, and other federal agencies.

**1971 Methylmercury poisoning in Iraq** The first major outbreak of methylmercury poisoning in Iraq, which was caused by the use of contaminated rice in the diet. This event led to the development of new methods for testing chemicals for toxicity.

**1970s Popularization of risk assessment** The use of risk assessment to evaluate the potential risks of chemicals to human health and the environment. This has led to the development of new methods for testing chemicals for toxicity.

**1983 The Red Book** The first federal law that required the registration of pesticides. It also provided for the control of their use.

**1980s Paradigm shift** The shift from a focus on the toxicity of individual chemicals to a focus on the toxicity of mixtures. This has led to the development of new methods for testing chemicals for toxicity.

**1980s PBPK modeling** The use of pharmacokinetic and pharmacodynamic modeling to evaluate the potential risks of chemicals to human health and the environment. This has led to the development of new methods for testing chemicals for toxicity.

**1980s Weight of evidence** The use of multiple lines of evidence to evaluate the potential risks of chemicals to human health and the environment. This has led to the development of new methods for testing chemicals for toxicity.

**1980 Health risk assessment of lead** The first federal law that required the assessment of the potential risks of lead to human health and the environment. This has led to the development of new methods for testing chemicals for toxicity.

**1990s Threshold of toxicological concern (TTC)** The use of TTC to evaluate the potential risks of chemicals to human health and the environment. This has led to the development of new methods for testing chemicals for toxicity.

**2008 Bovine spongiform encephalopathy and prion protein (BSE/PrP)** The first federal law that required the assessment of the potential risks of BSE/PrP to human health and the environment. This has led to the development of new methods for testing chemicals for toxicity.

**1950 Discovery of cytochrome P450 enzymes (CYPs)** The discovery of CYPs, which are enzymes that are involved in the metabolism of drugs and chemicals. This has led to the development of new methods for testing chemicals for toxicity.

**1960s Aerial science** The use of aerial science to evaluate the potential risks of chemicals to human health and the environment. This has led to the development of new methods for testing chemicals for toxicity.

**1960s Toxic solvents** The use of toxic solvents to evaluate the potential risks of chemicals to human health and the environment. This has led to the development of new methods for testing chemicals for toxicity.

**1971 Role of electrophilic intermediates in toxicologic intermediates** The use of electrophilic intermediates to evaluate the potential risks of chemicals to human health and the environment. This has led to the development of new methods for testing chemicals for toxicity.

**1970s Formaldehyde** The use of formaldehyde to evaluate the potential risks of chemicals to human health and the environment. This has led to the development of new methods for testing chemicals for toxicity.

**1970s Ames test** The use of the Ames test to evaluate the potential risks of chemicals to human health and the environment. This has led to the development of new methods for testing chemicals for toxicity.

**1976 Aryl hydrocarbon receptor (AHR)** The discovery of AHR, which is a receptor that is involved in the metabolism of drugs and chemicals. This has led to the development of new methods for testing chemicals for toxicity.

**1980s Alpha 2u globulin nephropathy** The use of alpha 2u globulin nephropathy to evaluate the potential risks of chemicals to human health and the environment. This has led to the development of new methods for testing chemicals for toxicity.

**1980s Nongenotoxic carcinogens** The use of nongenotoxic carcinogens to evaluate the potential risks of chemicals to human health and the environment. This has led to the development of new methods for testing chemicals for toxicity.

**1990s Omics** The use of omics to evaluate the potential risks of chemicals to human health and the environment. This has led to the development of new methods for testing chemicals for toxicity.

The supply of 1,000 posters was exhausted within hours of the opening of the conference. A free poster-sized version of the benchmarks is available by mail or download. (Image courtesy of Joseph Tart)

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## Dedication of new Tox21 robot system to test 10,000 chemicals for toxicity

By Robin Mackar

Key players involved in the Tox21 effort gathered March 10 at the NIH Chemical Genomics Center (NCGC) in Rockville, Md. to dedicate a new high-speed robot screening system. The addition of this robot system will enable the screening of a 10,000 chemical library for potential toxicity and marks the beginning of a new phase of the ongoing **Tox21** collaboration that is working to protect human health by improving how chemicals are tested in the United States.

NIEHS/NTP Director Linda Birnbaum, Ph.D., joined fellow institute director Eric Green, M.D., Ph.D., of the National Human Genome Research Institute (NHGRI), representatives from the U.S. Environmental Protection Agency (EPA) and the U.S. Food and Drug Administration (FDA), and key Tox21 staff to dedicate the new system and provide a tour to about

**Linked video:**

[Toxicity testing has entered the twenty-first century at NIH \(00:40\).](#)

(Launches in new window)

Download Media Player: Flash

40 invited guests. Tox21 includes a memorandum of understanding between the four agencies to more effectively predict how chemicals will affect human health and the environment. Among the guests were representatives from the U.S., European, and Korean committees for alternative testing methods.

Birnbaum and many of the other guests who came to the dedication immediately after the 50th anniversary meeting of the Society of Toxicology (SOT) held in Washington D.C., commented on how the ceremony added to the SOT experience.

“I can’t think of a better way to conclude SOT,” Birnbaum said. “This robot truly exemplifies a remarkable collaboration effort between four federal organizations that showcases how we can all bring our strengths and resources to the table to build the framework for a new predictive toxicology.”

The 10,000 chemical library to be screened by the robot system include compounds found in industrial and consumer products, pesticides, food additives, and drugs. A thorough analysis of more than 200 government and non-government databases of chemicals and drugs used in the United States and abroad was conducted to select the chemicals in this library. Testing results will provide information useful for evaluating whether these chemicals have the potential to disrupt human body processes enough to lead to adverse health effects.

In his remarks at the dedication, Green said, “Tox21 has used robots to screen chemicals since 2008, but this new robotic system is dedicated to screening a much larger compound library.”

The director of the NCGC at NHGRI, Christopher Austin, M.D., provided an overview of Tox21 efforts and added, “The Tox21 collaboration will transform our understanding of toxicology with the ability to test in a day what would take one year for a person to do by hand.”

NTP Biomolecular Screening Branch Chief Ray Tice, Ph.D., a key player in the Tox21 efforts for NIEHS/NTP is enthusiastic about the promise that new tools like this bring to the field. “By screening these chemicals for effects in key cellular pathways, we will gain a much better understanding of the relationship between chemicals, genes, pathways, and disease. This will enable us to better prioritize compounds for more comprehensive testing, to identify mechanisms of action, and ultimately to develop predictive models for adverse effects in humans.”



*The lead program staff from each of the four agencies involved in Tox21 take a break from their busy schedule to enjoy the robot cake. Shown left to right are Tice, Bob Kavlock, Ph.D., from EPA, Austin, and David Jacobson-Kram, Ph.D., from FDA. (Photo courtesy of NCGC)*



*Getting ready to cut the ribbon for the new dedicated robot are Green, Birnbaum, Woodcock, and Lek Kadeli, acting deputy assistant administrator for management in EPA’s Office of Research and Development. (Photo courtesy of NCGC)*

“Understanding the molecular basis of hazard is fundamental to the protection of human health and the environment,” said Paul Anastas, Ph.D., assistant administrator of the EPA Office of Research and Development. “Tox21 allows us to obtain deeper understanding and more powerful insights, faster than ever before.”

“This partnership builds upon FDA’s commitment to developing new methods to evaluate the toxicity of the substances that we regulate,” said Janet Woodcock, M.D., director of the FDA Center for Drug Evaluation and Research.

For b-roll clips from the NCGC facility, visit <http://www.genome.gov/27543670>.

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

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## Postdoctoral trainee launches career in health care communications

*By Archana Dhasarathy*

Sophie Bolick, Ph.D., left NIEHS recently for a position at MedThink Communications, a health care communications company in Raleigh, N.C. She spent the last four years as an Intramural Research and Training Award (IRTA) fellow with NIEHS Principal Investigator Jack Taylor, M.D., Ph.D., in the [Molecular and Genetic Epidemiology Group](#).

### The journey from pipetting to writing

At [MedThink Communications](#), Bolick will be placing aside her pipettes and will instead undertake various aspects of medical writing, including preparing abstracts, posters, and manuscripts.

Trained as a bench scientist, her transition to a writing career began in early 2010, when Bolick was exploring career options away from the bench. She decided to gain this experience by working with Eddy Ball, Ph.D., editor of the Environmental Factor. As readers of the newsletter will recall, she was a regular contributor, authoring one or two articles every month.

Along with her coverage of science events at NIEHS, Bolick also created a regular column of her own in the newsletter, featuring success stories about the trainees who transitioned to new careers.

“Sophie is good at what she does, she’s creative, and she meets deadlines. What more could an editor ask?” said Ball. “With the many trainee success stories that she wrote, it’s especially fitting that the newsletter is featuring a story about Sophie’s own career development path,” he added.

Bolick also worked with Environmental Health Perspectives science education and outreach program manager Bono Sen, Ph.D. With Sen’s encouragement, she taught a module in the “Teach the Teachers” workshop, and updated and summarized research articles for the classroom. “I enjoyed working with Sophie very much.



*During her time at NIEHS, Bolick also took advantage of training offered by the [Office of Fellows’ Career Development](#), headed by Diane Klotz, Ph.D. (Photo courtesy of Steve McCaw)*

I appreciated her initiative and her eagerness to learn new skills and broaden her skill set — very important for postdocs looking to enter into non-traditional fields,” said Sen.

These experiences at NIEHS earned Bolick encouraging reviews and positive comments from people, and she realized that she enjoyed writing. “There are a number of opportunities at NIEHS for fellows who want a career in science writing,” said Bolick. “Working with Eddy Ball and Bono Sen was great, because they are flexible about letting you work as little or as much as you want, without it interfering with your laboratory research,” she said.

### **Networking and mentoring play important roles in career success**

Bolick also credits her mentor, Taylor, with being very open-minded about letting her pursue her various interests outside the laboratory. “Without his support, it would have been very difficult for me to make use of these opportunities,” she said. Taylor concurred. “I think the key aspects of Sophie’s success were taking advantage of training opportunities and networking. Her active involvement in the [NIEHS Trainees Assembly \(NTA\)](#), the journal club, and ongoing participation in career fairs really helped her in thinking about, and developing a network to look for, job opportunities on a wider scale,” he said.

Developing a network played a major role in landing her the job at MedThink Communications. Bolick contacted Pratibha Hebbar, Ph.D., a former NIEHS trainee who worked at MedThink, for an informational interview to learn more about her job. And the rest, as they say, is history.

(Archana Dhasarathy, Ph.D., is a postdoctoral fellow in the Eukaryotic Transcriptional Regulation Group in the NIEHS Laboratory of Molecular Carcinogenesis)



*Taylor holds joint appointments in the NIEHS Laboratory of Molecular Carcinogenesis, where Bolick worked with him, and in the Epidemiology Branch. (Photo courtesy of Steve McCaw)*

## **A molecular epidemiologist at the bench**

Following her education in the Netherlands and Florida as a molecular biologist, Bolick switched to molecular epidemiology following her move to NIEHS. In Taylor’s laboratory in the Molecular and Genetic Epidemiology group, she analyzed global and gene-specific methylation as a determinant of breast cancer risk in the Sister Study, work currently in preparation for publication. Bolick also collaborated with the Bladder Cancer Consortium by contributing genotyping data acquired and analyzed using TaqMan assays.

In addition to research, Sophie found time to organize the journal club for the Laboratory of Molecular Carcinogenesis, teach a graduate level module on “The Molecular Basis of Cancer” at North Carolina Central University, chair a session of the Summers of Discovery Curriculum Planning Committee, and participate in a variety of NTA-sponsored activities. All of these activities, coupled with her research in the lab, helped her build a strong skill set and multidisciplinary knowledge base that prepared her for the career path of her choosing.

# NIMH director reaches out to NIEHS

By Ernie Hood

Director of the National Institute of Mental Health (NIMH) Thomas Insel, M.D., explored the topic of “Why NIMH Cares About NIEHS” during a presentation March 1 hosted by NIEHS/NTP Director Linda Birnbaum, Ph.D.

Insel told his audience that the two sister institutes have more in common than most would think, due to the growing evidence of links between environmental exposures and mental health. He also reached out for help from the environmental health sciences community in addressing an important public health issue by searching for answers to some of the most urgent questions in mental health research.

## A revolution in neuroscience

Insel began his remarks by describing the current profound shift in thinking about mental disorders. “We are in the middle of a revolution in neuroscience, particularly in our understanding of mental illness,” he said. “It requires a fundamental change in the way we think about the illnesses, even in the basic science that is the foundation for what we do.”

He noted that even with the extraordinary successes in biomedical research over the past half-century, none have involved the diseases of main concern to NIMH—schizophrenia, bipolar disorder, major depression, eating disorders, ADHD in children, and several other mental disorders. “I think by almost any measure of public health outcomes in terms of morbidity and mortality, we have failed on almost every one of the disorders for which we are responsible,” Insel added.

According to the sobering statistics Insel cited, mental disorders are the largest source of disability from all medical causes, a major cause of death, and one of the major drivers of health care costs, both inside and outside the system. The most recent estimate from 2008 is that direct and indirect costs of mental disorders total more than \$317 billion annually.

## An evolving paradigm in mental health

Although the track record is bleak, he explained, there are still reasons to be optimistic. “Part of the reason that we have failed in so many ways is because we haven’t thought about these disorders in the right way,”



*Insel expressed some concern about current public health outcomes in mental health, but told the NIEHS audience that new thinking about mental disorders offers hope for significant improvements. (Photo courtesy of Steve McCaw)*



*Insel’s talk attracted scientists from the Division of Intramural Research, such as Principal Investigator Paul Wade, Ph.D., right, as well as the National Toxicology Program, such as the Chief of the Cellular and Molecular Pathology Branch Robert Sills, D.V.M., Ph.D., left. (Photo courtesy of Steve McCaw)*

said Insel. “Much of the focus for the last century in thinking about serious mental illness has come from the standpoint of these being mental or behavioral problems which require mental or behavioral interventions... In the last decade or so, we’ve seen a completely different way of approaching these illnesses, and we think that offers real hope for transforming those kinds of statistics and moving the dial.”

### Potential areas for collaboration

Insel described the disruptive innovations taking place in mental health that profoundly influence the scientific approach being pursued at NIMH. He said that mental disorders are brain and developmental disorders that result from complex genetic risk plus experiential factors. Those disruptive innovations create a nexus with the types of research conducted by NIEHS, and Insel pointed to three areas where collaboration with NIEHS scientists could be productive:

- **Autism** — “This is not a rare disease anymore,” Insel claimed, and the considerable increase in prevalence in recent years cannot be explained simply by increased diagnosis. “What I would love your help with is figuring out what are the drivers here,” he said, noting that changes in epigenetics due to environmental exposures may be a major factor.
- **Military suicides** — Insel noted that military suicides have more than doubled over the past five years and now exceed combat deaths. Emerging research suggests that early trauma may be involved in later susceptibility, as developmental programming goes off-course.
- **The microbiome** — According to Insel, recent research in mice has shown that normal gut microflora modulate brain development and behavior, leading to intriguing hypothetical interfaces between the biology of the microbiome, neurophysiology, and human psychology. “It’s a place where NIMH would love to work with NIEHS,” said Insel, “as we think about how this whole area of biology affects the development of brain and behavior.”

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

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*NIEHS Deputy Director Richard Woychik, Ph.D., appeared contemplative as Insel described the common ground between the research agendas of the two institutes. (Photo courtesy of Steve McCaw)*



*Division of Extramural Research and Training program administrators, such as Kim McAllister, Ph.D., center, were interested in ways NIEHS and NIMH could collaborate in future grant programs. (Photo courtesy of Steve McCaw)*

# Environmental stewards hold annual meeting at NIEHS

By Eddy Ball

Continuing a five-year tradition, NIEHS hosted the North Carolina Environmental Stewardship Initiative (ESI) annual meeting March 11 in Robell Auditorium.

Gathered to review the year's accomplishments were companies and organizations from across North Carolina who are committed to improving their environmental performance beyond traditional levels of compliance, while at the same time improving performance, quality, safety, and, ultimately, the financial bottom line. NIEHS has been a member of [ESI](#), which is part of the North Carolina Department of Environment and Natural Resources (DENR), since 2005.

The day was filled with inspiring stories from representatives of businesses, governmental agencies, and organizations. But for NIEHS employees, the best came first, with remarks by NIEHS/NTP Director Linda Birnbaum, Ph.D., who was the first director to personally welcome attendees at the group's annual meeting. Birnbaum pointed to the Institute's long list of accomplishments in the area of environmental sustainability ([see text box](#)) and told her audience, "Public health and environmental health can't be separated."

Birnbaum spoke proudly of the united efforts of NIEHS/NTP employees, as the Institute prepares to apply for the more rigorous status as a Rising Steward, the second highest tier of membership in ESI. She also reinforced a central theme of the N.C. Division of Environmental Assistance and Outreach (DEAO) program — that sustaining the environment increases revenue for businesses and resources for governments and nonprofits, while helping create jobs.

## Honoring outstanding stewardship efforts

The program began with awards presented by N.C. DEAO Director Edythe McKinney, who facilitated the meeting, standing in for the secretary and assistant secretary of DENR. McKinney thanked NIEHS for its hospitality and said she hoped, "Next year's meeting will be held in our new "green" building [currently under construction in downtown Raleigh]."



*"Our mission here shares a lot of common ground with the goals of the ESI program," Birnbaum told attendees. "Preserving and protecting the public health is a basic pillar of environmental stewardship and sustainability." (Photo courtesy of Steve McCaw)*



*Merkle, center, listened as Birnbaum enumerated the progress NIEHS has made in the area of environmental sustainability. Sitting with him was Trish Castranio, HSB physical scientist and sustainability coordinator. (Photo courtesy of Steve McCaw)*

As she handed out awards to new and renewing ESI Partners and Rising Stewards, McKinney, a DENR veteran, joked about being “the new kid on this side of the block” in her role as meeting facilitator, and asked winners to briefly describe their environmental management activities. She recognized the following N.C. companies and organizations:

- Partners — Bridgestone Bandag Tire Solutions in Oxford, Domtar Paper in Plymouth, Freightliner in Cleveland, the N.C. Zoo in Asheboro, and Siemens Healthcare in Cary
- New Rising Stars — AW North Carolina in Durham, GKN Sinter Metals in Conover, John Deer Turf Care in Fuquay-Varina, and Smithfield Packing in Tarboro



*McKinney, left, presented Michael Young with an award for new partner Bridgestone Bandag. Young said he is especially interested in starting a monarch butterfly habitat on land adjacent to the company's facility in Oxford. (Photo courtesy of Steve McCaw)*

### **Sharing best practices for going green and lean**

As McKinney explained, an equally important part of the annual meetings is the opportunity to share, learn, and network. Attendees heard presentations by representatives of Fleet Readiness Center East, the N.C. Wildlife Federation's Wildlife and Industry Together (WAIT) program, the Corning Optical Fiber Wilmington facility, and Corning Cable Systems Hickory Cable Facility. Stewards, who occupy the highest and most demanding tier of ESI membership, came together for a panel discussion in the afternoon that explored the parallels between more efficient “lean” and more sustainable “green” manufacturing practices.

Presenters shared strategies for reducing water use, waste, and energy that collectively increased profits and resources many millions of dollars by reducing costs of production and operations as they improved their stewardship of the environment.

In several cases, integrating environmental, safety, production, and quality concerns in audits required for ISO certifications led to even greater savings as management improved its procedures.

Sustainability programs typically engage employees, encouraging them to become partners in the effort as they are forced to re-examine how to perform their duties more sustainably. Changes in procedure, such as reducing the use of a solvent by half, can result in significant reductions in material and waste disposal expenses, bring environmental benefits, improve quality, and make the workplace a safer place.



*Several rising steward representatives, such as Danny Miller of Fleet Readiness Center East in Cherry Point, discussed the ways reducing waste impacted the bottom line while helping the environment. Retraining painters at the facility, he said, reduced paint usage by 40 percent, saving \$80,000 annually. (Photo courtesy of Steve McCaw)*

## Environmental stewardship at NIEHS

Following her introduction by NIEHS Health and Safety Branch (HSB) Chief Scott Merkle who said, “We’ve never had a director who provided more support and commitment to environmental stewardship and sustainability,” Birnbaum welcomed ESI members to the Institute. She discussed NIEHS accomplishments and its ambitious plans for the future, as NIEHS strives to become a Rising Steward in the program:

- Instituting mandatory Environmental Management System training for all employees
- Diverting nearly 16,000 pounds of waste through composting or recycling nearly 95 percent of cafeteria waste
- Decreasing water use by some 40 percent since 2007 and increasing use of native plants
- Upgrading campus lighting fixtures and installing a solar collector, helping to reduce power usage in the Rall building by 25 percent since the late 1990s
- Becoming the first facility in Research Triangle Park to achieve WAIT certification and continuing efforts to preserve wildlife habitat
- Winning Green Champion Awards in 2010 for publishing the Institute’s first sustainability report and in 2009 for energy and water conservation initiatives at NIEHS facilities

And for future consideration:

- Installation of charging stations for electric vehicles and increasing the number of electric vehicles in the government fleet
- Upgrades for outside lighting to reduce power usage even more

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## University of Washington trainee headed to Lindau

*By Eddy Ball*

With sponsorship by her home State of Catalonia, Spain, trainee Judit Marsillach Lopez, Ph.D., will attend the prestigious [Lindau Nobel Laureate Meeting](#) June 26-July 1 in Germany. A fellow at the University of Washington (UW), Marsillach Lopez receives research support from NIEHS and holds a [Beatriu de Pinós Postdoctoral Fellowship](#) from the government of Catalonia, an autonomous region of Spain.

This summer, Marsillach Lopez will join approximately 25 Nobel laureates in physiology or medicine and some 550 other outstanding young researchers from throughout the world in a series of lectures, discussion sessions, and other activities designed to foster inter-generational scientific discourse.



**Linked video:**  
[Watch the Nature video, ‘The Spirit of Lindau’ \(16:00\)](#)

(Launches in new window)

Download Media Player:  Flash 

“I am honored by my selection,” Marsillach Lopez said of the upcoming meeting, “and I am proud to be representing the people of Catalunya [Spanish for Catalonia] at this international event.”

### NIEHS support for genetic research

Marsillach Lopez is a member of the UW lab headed by [Clement Furlong, Ph.D.](#), professor of genome sciences and of medicine in the Division of Medical Genetics. The group studies the genetic variability of insecticide metabolism and sensitivity in humans. Marsillach Lopez’ research on paraoxonase (PON1), a high-density lipoprotein (HDL)-associated enzyme that inactivates the toxic metabolites of several organophosphate pesticides (OP) and nerve agents ([see text box](#)), has received support from three NIEHS grants to UW:

- [Structure and Function of the Human PON1 Polymorphism](#) — Furlong, principal investigator (PI)
- Superfund Research Program [Effects-Related Biomarkers of Environmental Neurotoxic Exposures](#) — Harvey Checkoway, Ph.D., PI
- [Center for Child Environmental Health Risks Research](#) — Elaine Faustman, Ph.D., PI



*“It was my interest in this enzyme that took me to Seattle at the end of 2009 [to work with] Dr. Furlong, who is one of the top scientists studying PON1,” said Marsillach Lopez, shown here in the bleachers above the UW Husky stadium. (Photo courtesy of Judit Marsillach Lopez)*



**Linked video:**  
[Watch as Furlong discusses his research into biomarkers of exposure to OP \(58:15\)](#)

(Launches in new window)

Download Media Player: [Quicktime](#)

### What promises to be a week to remember

As one of what the Lindau organizers describe as “international Best Talents,” Marsillach Lopez will participate in an activity-filled week of social and intellectual interaction among laureates and students living, eating, and talking together in and around the historic island city of Lindau. The city sits on the shore of Lake Constance, the Bodensee, where the borders of Germany, Austria, and Switzerland meet.

The Lindau meetings began in 1951 as a sort of reunion for expatriate German scientists who left their country during the Nazi period. From the outset, organizers envisioned the meeting as a nonideological gathering of inquiring minds dedicated to transferring knowledge between generations.



*Furlong said of his protégée, “Judit is an outstanding young scientist, and I’m certain she’ll return to Seattle overflowing with new perspectives on science and society. This program certainly represents a wise investment in the next generation of leading scientists.” (Photo courtesy of Clement Furlong and the University of Washington)*

## Understanding host response to environmental exposures

The Furlong lab studies the molecular basis of the genetic polymorphism in human plasma paraoxonase 1 (PON1) that specifies high or low metabolism of organophosphate (OP) insecticides and nerve agents. Low levels of this enzyme are also a risk factor for cardiovascular disease.

Since joining the Furlong group, Marsillach Lopez has worked on several NIEHS-funded projects. One of the first projects is focused on characterizing biomarkers of exposure to OP insecticides. Her group successfully developed rapid immunomagnetic bead protocols for purifying biomarkers that are modified by OP exposure, butyrylcholinesterase (BChE) and acylpeptide hydrolase (APH). Using mass spectrometry, the team identified specific adducts to the active-site serines in these proteins.

Another project is related to the structure and function of human PON1 and producing recombinant variants of PON1 to better understand the function of this multi-tasking enzyme. One goal of these studies is to generate recombinant PON1 molecules with much higher catalytic efficiencies of OP hydrolysis that can be used to treat cases of OP poisoning, such as nerve agent exposure and exposure to OP insecticides for which the catalytic efficiency of the native PON1 is too low to protect a person from the exposure.

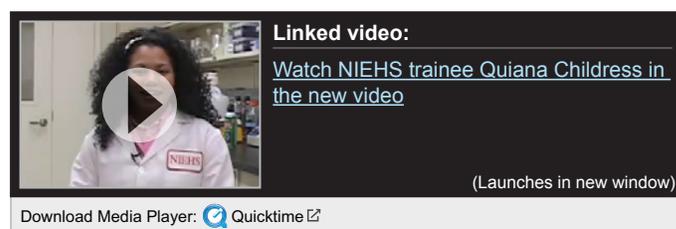
Furlong's group is also generating variants of human PON1 that have been associated with amyotrophic lateral sclerosis (ALS) — Lou Gehrig's disease — to better understand the properties of the variant proteins. To that end, the researchers are striving to improve purification protocols for PON1. Using anti-PON1 antibodies generated in rabbits, they have been able to purify PON1-containing HDL particles in a single step. These protocols will allow them to examine the proteomics of PON1-containing HDL from healthy and diseased individuals and better understand the role of PON1 in diseases such as cardiovascular disease and ALS.

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## Young NIEHS fellow featured in new video

*By Matt Goad*

NIEHS is playing a part in the remarkable story of Quiana Childress, a young woman who went from being homeless in rural Arkansas to graduating from college, pursuing her dream of becoming a doctor, and starring in a new video produced by her sorority to help raise funds for scholarships.



A recent graduate of the University of Arkansas at Pine Bluff (UAPB), Childress has applied to medical school and is anxiously awaiting acceptance. While she waits, Childress is working as a research fellow at NIEHS.

Alpha Kappa Alpha Sorority, Inc., Childress' sorority at UAPB, which awarded her an [Educational Advancement Foundation](#) \$25,000 scholarship for medical school, commissioned a video to be made about her story, and two other AKA scholars. A videographer came from Chicago to shoot footage of Childress at the NIEHS main campus in Research Triangle Park, N.C.

Childress previously served as the AKA Alpha Rho chapter vice president and Arkansas undergraduate cluster coordinator for the organization.

“My time at NIEHS has been tremendously helpful, allowing me to really develop my scientific thought process and research skills,” said Childress. “I get to use some of the latest equipment in research and work with some of the best colleagues who continue to push me to excel.” She credits Stavros Garantziotis, M.D., her NIEHS mentor, with helping her learn to think like a researcher.

Garantziotis said Childress has the right qualities for an excellent medical career. “She is a remarkably level-headed, personable, and mature young woman,” Garantziotis said. “She also brings with her other qualities, such as empathy, compassion, and a keen insight into the human condition. No doubt her life experiences have informed these qualities. These qualities, together with her intellect, moved me to recruit her to my lab.”

First lady Michelle Obama, the UAPB commencement speaker last May, singled out Childress at the graduation ceremony as an example of triumph over adversity.

When Childress was only 16 years old, she became homeless. The teenager lived out of a car, as she struggled to finish high school while also working two jobs. Childress said she would usually wake up at 3:00 a.m. to study.

Knowing that she would have a hard time paying her way through college, even with scholarships, Childress completed a one-year licensed practical nursing (LPN) program before enrolling at UAPB. As a college student, she worked at a nearby all-male maximum security prison, where she became an inspiration to the inmates.

“Some of the guys,” Childress said, “they came up to me and they said, ‘You inspire us. We didn’t all quite have it that bad and we took alternate routes. But you didn’t.’”

For most people, college and work would be a big enough challenge, but Childress said she also volunteered for American Red Cross and the Pine Bluff Boys and Girls Club, and chartered two organizations, the Doc Jones Forensic Science Team and the UAPB School of Arts and Science Student Advisory Council. She also took advantage of research opportunities in Alaska, at Yale University School of Medicine, and received a NASA/Arkansas Space Grant Consortium grant.

In 2010, Childress graduated *summa cum laude* — with the highest grade point average in the School of Arts and Sciences — with a bachelor’s degree in biology.

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

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*After Childress’ graduation last year, her story gained national attention. (Photo courtesy of Steve McCaw)*

# NIEHS participants at upcoming NAS workshop on the microbiome

By Eddy Ball

NIEHS is playing a major role as sponsor and participant in the upcoming workshop on “[Interplay of the Microbiome, Environmental Stressors, and Human Health](#),” April 27-28 at the 20 F Street Conference Center, NW, in Washington, D.C. The workshop is part of the National Academy of Science’s ongoing [Emerging Science for Environmental Health Decisions](#) series.

Representing NIEHS will be Senior Advisor for Public Health [John Balbus, M.D.](#), chair of government liaisons for the series, and Lisa Helbling Chadwick, Ph.D., a health scientist administrator in the Cellular, Organs, and Systems Pathobiology Branch.

Balbus will deliver opening remarks and moderate a panel discussion during a session devoted to “Interplay of Environmental Exposures and the Microbiome,” along with NIEHS grantee [Ivan Rusyn, M.D., Ph.D.](#), of the University of North Carolina at Chapel Hill. Chadwick will participate in a panel discussion during the session, exploring “Societal, Research, and Public Policy Implications.”

NIEHS grantee [Helmut Zarbl, Ph.D.](#), will present opening and closing remarks at the workshop. Zarbl is director of the NIEHS-funded Center for Environmental Exposures and Disease at the University of Medicine and Dentistry of New Jersey/Rutgers University.

The workshop is free and open to the public. [Registration](#) is open through April 26.



*Balbus is one of three high-profile NIEHS special advisors headquartered at the NIEHS office in Bethesda, Md. (Photo courtesy of Steve McCaw)*



*Helbling Chadwick will articulate NIEHS priorities in the areas of research and public policy. (Photo courtesy of Steve McCaw)*



*Rusyn’s research interests include bioinformatics, genetics, and toxicology. He is shown at an earlier conference on bioinformatics and toxicology at North Carolina State University. (Photo courtesy of Steve McCaw)*



*Zarbl is a member of the workshop series’ steering committee. (Photo courtesy of Helmut Zarbl)*

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# Mark your calendars for the NIEHS career fair

By Sindura Ganapathi

The 14th annual NIEHS Biomedical Career Fair will be held April 29 at the U.S. Environmental Protection Agency conference center in Research Triangle Park, N.C.

The annual career fair is one of the largest assemblies of biomedical organizations and young scientists in the Triangle area. It targets postdoctoral fellows and advanced graduate students, providing these young scientists an opportunity to explore a myriad of fields, share experiences and ideas, and create a contact network as they plan for their future careers in the biomedical sciences.

This year's career fair will feature a keynote address by [Shirley Malcom, Ph.D.](#), who is the head of Education and Human Resources at the American Association for the Advancement of Science (AAAS).



*A tireless advocate of STEM (scientific, technical, engineering, and mathematical) education and diversity, Malcom has a long list of honors to her credit, including the Public Welfare Medal of the National Academy of Sciences, which she received in 2003. (Photo courtesy of AAAS)*



**Linked video:**  
[Watch as Malcom discusses 'Scientific Literacy for All' \(0:56\)](#)

(Launches in new window)

Download Media Player: [RealPlayer](#)

The event will also feature workshops and discussion panels, one-on-one CV/Resume review, company exhibits, and other career-related events.

For more information and to register as a participant or exhibitor, visit the Career Fair Web site at [www.niehs.nih.gov/news/events/highlight/careerfair/index.cfm](http://www.niehs.nih.gov/news/events/highlight/careerfair/index.cfm).

(Sindura Ganapathi, Ph.D., is an Intramural Research Training Award fellow in the NIEHS Laboratory of Signal Transduction Inisotal Signaling Group.)

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# Science Notebook

## NIEHS scientists join forces with green chemists

By Thaddeus Schug

NIEHS/NTP scientists joined forces with leaders in the field of green chemistry in what may turn out to be a groundbreaking meeting, “Green Chemistry and Environmental Health Sciences — Designing Endocrine Disruption Out of the Next Generation of Materials,” held March 21-23 in Sausalito, Calif.

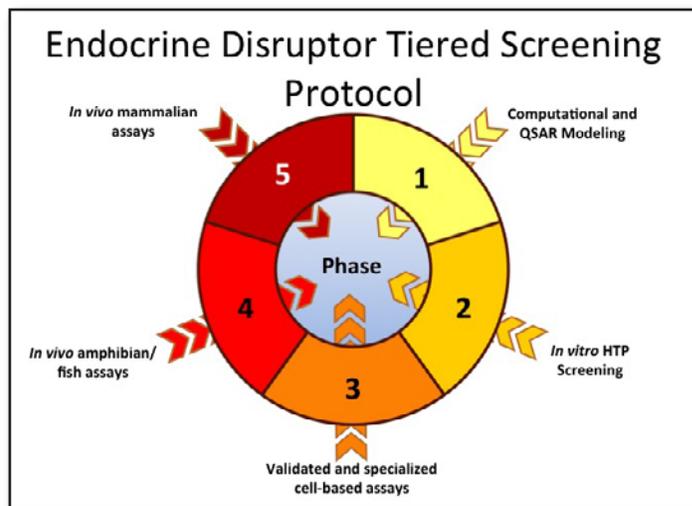
The challenges facing scientists trying to design such new materials are daunting. Say a chemist has developed a compound that he or she believes could be a replacement for bisphenol A (BPA). How will the scientist determine if the molecule is safer to human health and the environment? What testing will need to be done and what will guide scientists through this process?

The goals of the meeting in Sausalito were ambitious — to develop a consensus statement on the principles that guide the science needed to assess risks of potential endocrine disruptors, and to develop a reliable and rational testing protocol to aid chemists as they develop and bring the next generation of chemicals into the marketplace.

### The intersection of green chemistry and environmental health science

Karen O’Brien, Ph.D., from Advancing Green Chemistry (AGC) and Pete Myers, Ph.D., of Environmental Health Sciences (EHS), welcomed participants to the event, which brought together an equal mix of biologists and chemists. Representatives from NIEHS and NTP included Division of Extramural Research and Training (DERT) program administrator Jerry Heindel, Ph.D., and Kristina Thayer, Ph.D., director of the NTP Center for the Evaluation of Risks to Human Reproduction (CERHR).

Following a social ice-breaking exercise on the evening of March 21, the first full day of the meeting opened with presentations from Terry Collins, Ph.D., the Teresa Heinz Professor of Green Chemistry at Carnegie Mellon University, and John Warner, Ph.D., president and founder of the Warner Babcock Institute for Green Chemistry.



*A representative diagram of the draft screening protocol unveiled at the meeting. The protocol is designed in a tiered approach, with rapid and cost effective screens conducted in the early phases and more extensive testing toward the end. (Slide courtesy of Pete Myers)*



*Left to right, Collins, Heindel, and Warnermix ingredients for a batch of salmon tartare. The cooking exercise was used as an ice-breaking event to demonstrate how environmental health scientists and chemists can work together to solve complex issues. (Photo courtesy of Pete Myers)*

Both Collins and Warner stressed the need for fundamental changes in the way that scientists design new chemicals and the process of bringing them into the marketplace. “We must also pay close attention to the environmental impact and the effects on human health posed by these chemicals, and for those reasons chemists need to work hand-in-hand with biologists,” said Warner. He also stressed that chemists generally have no background in toxicology, but that they need to be able to test the chemicals being developed for endocrine activity and to do it early on in the product development process.

### Designing a chemical screening protocol

The remainder of the day was divided into discussion sessions covering each phase of a newly developed screening model, designed by a science advisory board formed by meeting organizers that met monthly, via teleconference, for six months prior to the workshop. The protocol is geared towards identifying a wide-range of endocrine-active chemicals, such as atrazine, BPA, brominated flame retardants, organotins, perchlorates, and phthalates. The Board conducted interviews with scientists with expertise in specific areas of toxicology, endocrine disruption, and assay development.

The testing paradigm proposed involves a five-tiered approach, starting with the fastest and cheapest assays and working through more specialized tests to determine whether a new chemical has endocrine disrupting characteristics. The initial two phases rely on predictive computer modeling and high-throughput screening to quickly weed out problem chemicals. These tests are followed by more specific *in vitro* cell-based screening assays with a mind to refining, reducing, and replacing animal testing as much as possible.

The final two phases involve use of fish, amphibian, and mammalian *in vivo* modeling systems. Overall, the protocol is intended to help green chemists establish a high degree of confidence that the replacements they are developing are unlikely to be harmful to humans or the environment.

### The next steps

The meeting wrapped up with discussion on how to proceed with development of the testing protocol as well as plans for implementation. The advisory board plans to use input from the meeting to develop and publish a white paper outlining guidelines that chemists can use to assess the quality of protocols and tests used to assess endocrine disruption.



*Laura Vandenberg, Ph.D., left, contributes to the discussion on assay development, as Tom Zoeller, Ph.D., center, and Wim Thielemans, Ph.D., look on. Vandenberg, a postdoctoral fellow at Tufts University, studies the developmental effects of endocrine disrupting chemicals. (Photo courtesy of Pete Myers)*



*Left to right, Bruce Blumberg, Ph.D., Thayer, and Andreas Kortenkamp, Ph.D., served as panel members for a discussion on *in vitro* screening assays. (Photo courtesy of Pete Myers)*



*A group photo of the meeting attendees. The meeting was held at the Cavallo Point Lodge, which sits adjacent to the Golden Gate Bridge. (Photo courtesy of Pete Myers)*



*NIEHS grantees Andrea Gore, Ph.D., left, and Frederick vom Saal, Ph.D., were among panel members for the discussion on in vivo assays. Both Gore and vom Saal are members of the project's scientific advisory board. (Photo courtesy of Pete Myers)*

(Thaddeus Schug, Ph.D., is a postdoctoral research fellow currently on detail as a program analyst in the NIEHS Division of Extramural Research and Training. He was part of the NIEHS/NTP delegation and a presenter at the meeting.)

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## Emerging Environmental Health Science in Green Chemistry

NIEHS Senior Advisor for Public Health John Balbus, M.D., attended the inaugural symposium March 24 for the new University of California, Berkeley Center for Green Chemistry, entitled “Green Chemistry: Collaborative Approaches and New Solutions.” Balbus’ talk, “Incorporating Emerging Environmental Health Science in Green Chemistry,” outlined some of the challenges of applying 21st century science to protect public health.

- How do we harness the potential of unlocking the genome?
- Can we more accurately predict which chemicals are likely to cause harm?
- How do we implement our understanding of susceptibility and non-chemical stressors to enhance human health?
- How can we better incorporate new methods and technologies into science policy?

Balbus proposed that the newly developed **Tox21**, an interagency high throughput screening initiative, is aiming to meet many of these challenges and could be a valuable tool for green chemists. Demonstrating its utility in screening chemicals for disruptions in insulin signaling, Balbus concluded, “Advancements in programs such as Tox21 will eventually allow us to accurately predict how chemicals will impact human health before they are brought into the marketplace.

# Fry outlines a systems level approach to understanding arsenic

By Melissa Kerr

Arsenic has a worldwide reputation as a poison, but research has also shown it to be an effective treatment for cancer. During a seminar at Duke University Feb. 25, NIEHS grantee Rebecca Fry, Ph.D., explored both aspects of this chemical as part of the Integrated Toxicology and Environmental Health (ITEH) Seminar Series.

Fellow NIEHS grantee Ed Levin, Ph.D., welcomed Fry and hosted her presentation, “A Systems Level Approach to the Two Faces of Arsenic: Cancer Causation, Cancer Treatment.” Fry is an assistant professor in the Environmental Sciences and Engineering department at the University of North Carolina at Chapel Hill (UNC-CH) and an NIEHS Outstanding New Environmental Scientist awardee. Levin is director of the Training Core of the Duke University Superfund Research Center.

## The face of a medicine

Fry opened with a discussion of Trisenox, a clinical version of arsenic trioxide that has been successfully used to treat acute promyelocytic leukemia. This cancer affects blood and bone marrow and is caused by a gene created by a particular translocation of two chromosomes. Trisenox cleaves the gene, Fry explained, so that the cancer can be effectively treated. To identify novel mechanisms by which arsenic may influence tumor growth, Fry and her team examined data representing differential responses of 60 different tumor cell lines to arsenic trioxide. They found a striking range of responses, from a high level of sensitivity in leukemia cells to far more resistance in colon cancer cells.

In Fry’s search for specific genes that underlie sensitivity of tumor cells to arsenic trioxide, she and her team found that the pathway of NRF2, a transcription factor involved in cell survival signals, had significantly higher expression within the arsenic-resistant cell lines. Through this association and subsequent laboratory testing, she established that by controlling NRF2 expression, “We can change a tumor cell that is resistant to arsenic trioxide to one that is sensitive to arsenic trioxide-induced killing.”



*As her studies progress, Fry said she looks forward to “really digging down into the effects of early-life exposure to arsenic and long-term health consequences.” (Photo courtesy of Steve McCaw)*



*Duke’s ITEH Seminar Series of lectures are well attended by students and faculty with interest in environmental health issues. (Photo courtesy of Steve McCaw)*

## The face of a poison

Fry also highlighted the second face of arsenic, that of a cancer causing agent. Inorganic arsenic is considered a Group 1 carcinogen by the International Agency for Research on Cancer. Chronic exposure results in cancer of the skin, bladder, and liver, among others. Although the U.S. Environmental Protection Agency (EPA) limit for arsenic is 10 parts per billion (ppb), Fry explained, “More than 40 million people in Southeast Asia alone are exposed to greater than 50 ppb, a level that dramatically increases cancer risk.”

Another disturbing discovery was that exposure to arsenic prenatally increased the chance of acquiring cancer, even if the subject was not exposed chronically after birth. According to Fry, the nuclear factor-kappaB (NF- $\kappa$ B) pathway, a pathway that regulates inflammatory responses, is impaired in children prenatally exposed to the chemical.

Fry said that a major thrust of her research is to understand cellular mechanisms that control the gene expression change in that pathway. She cited evidence that arsenic is associated with epigenetic modifications in gene expression. To that end, she is looking at DNA methylation of cytosine ([see text box](#)).

## Silencing tumor suppressor genes through DNA methylation

Fry’s research probes the epigenetic consequences of arsenic exposure in human populations. Methyl groups, when attached to specific bases, result in a modification in gene expression. Fry has focused her attention on CpG (cytosine-phosphate-guanine) islands within the DNA. The methylation of CpG sites is associated with gene silencing.

“Gene members of the NF- $\kappa$ B pathway,” Fry explained, “are enriched for differential methylation,” highlighting epigenetic modification in people with signs of arsenic poisoning. Her group identified 17 tumor suppressor genes with increased hypermethylation in the subjects with arsenicosis.

Fry’s research suggests that arsenic exposure leads to dramatic changes in epigenetic programming. “These changes could well link arsenic to increased mortality from lung cancer and liver cancer.” Fry will continue to examine the role of these epigenetically altered sites as biomarkers of exposure and disease.

Building on earlier studies in Thailand, Fry’s current research follows people in the Zimapan Valley of Mexico who consume arsenic-contaminated water. Up to 34 percent of this population have arsenic-induced skin lesions, and arsenic levels there can reach as high as 1,000 ppb — 100 times the EPA and World Health Organization limits. Her team collaborates with UNC-CH biochemist Miroslav Styblo, Ph.D., also an NIEHS [grantee](#), to answer a central question: “If we look across the genome, can we find novel genes that are epigenetically altered and associated with arsenic exposure?”

Fry’s results show that as the exposure to arsenic increased, the level of DNA methylation increased in 182 out of 183 candidate genes. Strikingly, the results show again the NF- $\kappa$ B pathway to be differentially methylated in adults with signs of arsenic poisoning. Her work establishes a new connection between the hypermethylation of several tumor suppressors and chronic arsenic poisoning or arsenicosis.

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

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# Microglia: A complex resident immune cell of the brain

By Emily Zhou

NIEHS Principal Investigator [Jean Harry, Ph.D.](#), examined the complex processes of neuroinflammation in the brain during a talk March 4 before an audience of students and faculty gathered at Duke University.

Harry is the head of the Neurotoxicology Group in the NIEHS Laboratory of Toxicology and Pharmacology. She stressed the importance of understanding the different patterns of activation of microglia as a defense mechanism against disease processes in the brain, such as inflammation, trauma, ischemia, tumor, neurodegeneration, and neurotoxicity.

“The take-home message” of her seminar, said Harry, “is that morphological phenotypes of microglia contribute to the identification and understanding of multiple and shifting roles of microglia from neurotoxicity to neuroprotection.” She also emphasized, “Targeting of therapeutic interventions requires an understanding of all interdependent processes of neuroinflammation and microglial function.”

## Neuroinflammation is associated with different cellular mechanisms

Neuroinflammation occurs following numerous injuries and diseases, such as traumatic brain injury, vascular damage, sclerosis, autism, brain tumor, bipolar disorder, schizophrenia, Parkinson’s disease, Alzheimer’s disease, Huntington’s disease, and environmental exposures to organic mercury, tin compounds, and lead.

Neuroinflammation is a highly complex process associated with different cellular mechanisms involving tumor necrosis factor alpha (TNF- $\alpha$ ). A critical component lies in discriminating between the contribution of resident microglia, the immune cells of the brain, and the contribution of the infiltrating macrophage associated with damage to the blood-brain-barrier.

Referring to an immunofluorescence image of a brain stained for various cellular markers after trauma, Harry pointed out the problem: “Are we looking at [neuroinflammatory] responses from the resident cells of the brain or are we looking at modified cells now that are macrophages that have components of peripheral macrophages?” She cautioned, “Within any disease state or experimental model, multiple cellular processes are occurring at any one time.” According to Harry, it’s imperative that multiple markers both for inflammation and for other cellular events be examined to interpret the impact of a microglia response.



*Harry’s hypothesis challenges longstanding conventional wisdom about microglia, which she says can actually change function in response to different kinds of injury, environmental exposure, and disease. (Photo courtesy of Steve McCaw)*



*Levin is a gracious host who often takes advantage of talent from nearby universities, NIEHS, and the U.S. Environmental Protection Agency for the weekly ITEHP Lecture Series presentations. (Photo courtesy of Steve McCaw)*

## Microglia: morphology, activation, and function

Microglia are resident cells of the central nervous system (CNS) that play an important role in removal of cellular debris and aberrant proteins. They serve to repair vascular damage, contribute to synaptic stripping and remodeling, directly communicate with neurons, and change expression of anti-oxidant proteins in astrocytes for protection. “It’s very possible,” said Harry, “that dysregulation of microglia contribute to chronic neuroinflammation, but also [result] in a deficit in repair response.”

Ongoing research in Harry’s laboratory examines an *in vivo* model of brain injury to identify resident microglia heterogeneity and the presence of cellular markers that will indicate the inflammatory characteristics of the microglial response and the shift to a neuroprotective phenotype. When activated, microglia undergo morphological changes from a ramified morphology, to a retraction of processes, and finally to a rounded, ameboid shape.

Harry presented data supporting the hypothesis that these changes correspond with functional changes of the microglia and suggested that a closer examination of the morphological heterogeneity of microglia in injury and remodeling will assist researchers in understanding the multiple contributions of these cells and provide insight into therapeutic intervention.

“The resident immune network of the brain coordinates a diverse array of intra-neural protective host responses as well as pathogenic responses to regulate complex processes of initiation, propagation, and suppression of immune and inflammatory responses,” Harry explained.

This process is normally tightly regulated, she continued, “[but] under pathological states, the immune responses are spatially and temporally dysregulated, leading to detrimental consequences.” In such cases, simple downregulation of these signals and microglia does not provide neuroprotection, but rather exacerbates the injury, suggesting an alternate neuroprotective role of microglia.

Harry’s talk was part of the Duke [Integrated Toxicology and Environmental Health \(ITEHP\) Program](#) seminar series. [Edward Levin, Ph.D.](#), who hosted Harry, is a professor of psychiatry and psychological and brain sciences at Duke. ITEH is supported in part by the NIEHS Superfund.

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



*Annette Kirshner, Ph.D., a health scientist administrator in the Cellular, Organs and Systems Pathobiology Branch of the NIEHS Division of Extramural Research Training, made the trip to Durham for Harry’s seminar. (Photo courtesy of Steve McCaw)*

### Cascade of responses in neuroinflammation

Just like any inflammation, when neuroinflammatory response is initiated, it is characterized by an induction of a pro-inflammatory response and classical macrophage activation. It is then followed by expression of anti-inflammatory cytokines and the initiation of negative feedback pathways to down-regulate pro-inflammatory signaling pathways. The overall result is repair, resolution, and return to tissue homeostasis. Chronic inflammation, however, undermines these checks and balances to control the innate immune response and may result in recruitment of peripheral immune cells for assistance. This can lead to a concurrent expression of pro-inflammatory cytokines and those associated with repair, which will make it difficult to identify target sites for therapeutic regulation.

## Trainees honored for scholarship and service by SOT

By Eddy Ball

Four NIEHS/NTP trainees returned home from the 50th anniversary meeting of the Society of Toxicology (SOT) with honors for their exceptional scholarship and service to the field of toxicology.

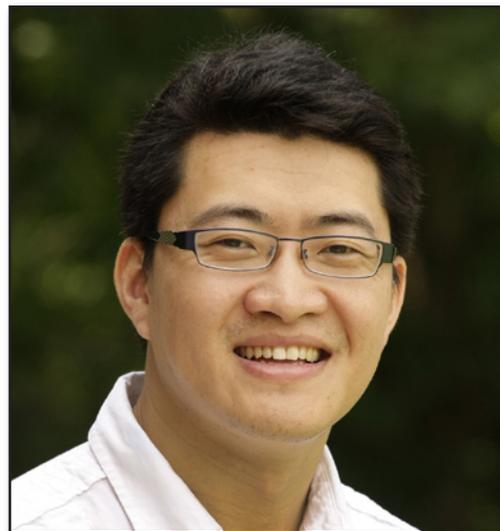
In addition to Zhengyu Yin, Ph.D., a visiting fellow in the NIEHS Cell Biology Group whose SOT Carcinogenesis Specialty Section Postdoctoral Fellowship Award was announced last month ([see story](#)), the following trainees also received 2011 awards from SOT Specialty Sections and Special Interest Groups:

- Xiaoqing Chang, Ph.D., a visiting fellow in the NTP [Biomolecular Screening Branch](#) headed by Raymond Tice, Ph.D., won the [Nanotoxicology Specialty Section](#) Outstanding Postdoc Award for her abstract, “A physiologically based pharmacokinetic (PBPK) model of micro- and nano-sized fluorescent polystyrene spheres in rats.” Co-authors on the study include her first mentor at NIEHS, former Special Advisor Chris Portier, Ph.D., and NTP scientist Nigel Walker, Ph.D. Her current mentor in the NTP is Michael DeVito, Ph.D., who nominated Chang for her award.

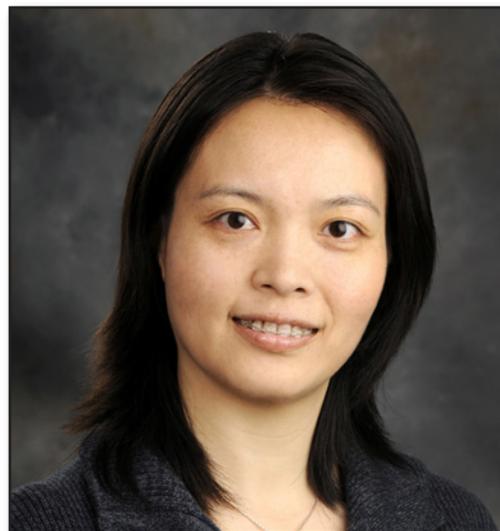
According to Chang, the model adequately describes the kinetics of both micro and nano polystyrene spheres and clearly demonstrates that the size of these particles influenced their kinetics. This research provides a general framework for elucidating the kinetics of nanoparticles and should greatly enhance understanding of nanotoxicity and improve risk assessment of nanotechnology in the near future.

- [Saurabh Chatterjee, Ph.D.](#), visiting fellow in the NIEHS Free Radical Metabolism Group headed by Principal Investigator Ron Mason, Ph.D., won the Young Investigator Endowment Award from the [Association of Scientists of Indian Origin](#) Special Interest Group for his abstract, “Synergism of leptin signaling and post-translational protein oxidation in bromodichloromethane exposure is key to the development of steatohepatitis [inflammation of liver] of obesity.”

Chatterjee’s research is related to the mechanisms of potentiation of hepatotoxicity of a disinfection byproduct of drinking water in obese mice. He is investigating the role of reductive free radical formation that happens when some toxins are metabolized within the liver by cytochrome P-450 to trigger an inflammatory cascade, resulting in progression from fat accumulation to steatohepatitis and other complications.



Zhengyu Yin (Photo courtesy of Steve McCaw)



Xiaoqing Chang (Photo courtesy of Steve McCaw)



Saurabh Chatterjee (Photo courtesy of Saurabh Chatterjee)

- [Minerva Mercado-Feliciano, Ph.D.](#), an Intramural Research Training Award fellow in the NTP Toxicology Branch headed by Paul Foster, Ph.D., was presented with an award for outstanding service by the [Hispanic Organization of Toxicology \(HOT\)](#) Special Interest Group. She was recognized for her contributions as editor of the official SOT-HOT newsletter, *Toxenlaces*, which began publication in 2009.

*Toxenlaces* provides Hispanic toxicologists in the United States and the international Spanish and Portuguese-speaking scientific communities with information about important toxicological events and issues occurring in their countries. The newsletter serves as toxicology forum and disseminates critical dates for events, health perspectives, and funding and training opportunities.

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*Minerva Mercado-Feliciano (Photo courtesy of Steve McCaw)*

## Research fellow shines at drug development meeting

*By Eddy Ball*

NIEHS research fellow Xueqian (Shirley) Wang, Ph.D., received a first-place prize for her poster presentation at the [Research Triangle Park Drug Metabolism Discussion Group](#) 2011 Winter Symposium, March 17 at the Hilton Raleigh-Durham Airport in Research Triangle Park, N.C. Wang presented the findings of her recent research, “Activating PKC [protein kinase C isoform] Beta1 at the Blood-Brain Barrier Reverses Induction of P-glycoprotein (Pgp) Activity by Dioxin and Restores Drug Delivery to the CNS.”

For the past four years, [Wang](#) has been a member of the NIEHS Laboratory of Toxicology and Pharmacology Intracellular Regulation Group, headed by Principal Investigator and acting Scientific Director [David Miller, Ph.D.](#) Miller and a former postdoctoral fellow in the group, Brian Hawkins, Ph.D., were co-authors on the study.

As part of the group, Wang has investigated the biology of Pgp, an ATP-driven drug efflux pump that is highly expressed at the blood-brain barrier (BBB), where it performs an important protective function by limiting the transport of environmental toxicants into the central nervous system (CNS). However, induction of Pgp can also impede the delivery of therapeutic drugs for treating CNS disorders and for effectively reducing pain in as many as 30 percent of patients.



*Wang said that the next step in her work will be looking into the role of the Nrf2 protein in regulation of Pgp and other ATP-binding cassette (ABC) transporters. (Photo courtesy of Steve McCaw)*

### Enhancing drug delivery

The Miller group has explored ways of targeting signals that increase Pgp expression at the BBB in order to create windows of opportunity for enhancing the transport of therapeutic drugs through the tight barriers in the endothelial cells lining the capillaries within the brain. The researchers are searching for a short-duration intervention along the Pgp activation pathway, so that drug delivery can be improved without leaving the CNS vulnerable any longer than necessary.

In this latest series of experiments, Wang, Hawkins, and Miller investigated whether PKCbeta1-based signaling can reverse CNS drug resistance caused by aryl hydrocarbon receptor (AhR)/dioxin induction of Pgp expression.

The researchers exposed freshly isolated rat brain capillaries to a form of dioxin known as TCDD, which more than doubled Pgp and significantly reduced brain uptake of the drug verapamil, a Pgp substrate. The team then perfused the brain vasculature of the exposed rats with a compound known as dPPA, which specifically activates PKCbeta1.

They determined that this activation at the BBB both reduced basal Pgp activity and reversed the increase in activity triggered by AhR induction of transporter expression. This intervention thus improved brain uptake of verapamil, suggesting that targeting PKCbeta1 may be an effective strategy for improving drug delivery to the brain, even for drug-resistant patients.

In addition to her winning poster, Wang has received several awards in recognition of her research at NIEHS, including NIH Fellows Awards for Research Excellence (FARE) in 2009 and 2010, as well as two first place prizes from the Society of Toxicology in 2010.

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## NIEHS investigators find link between DNA damage and immune response

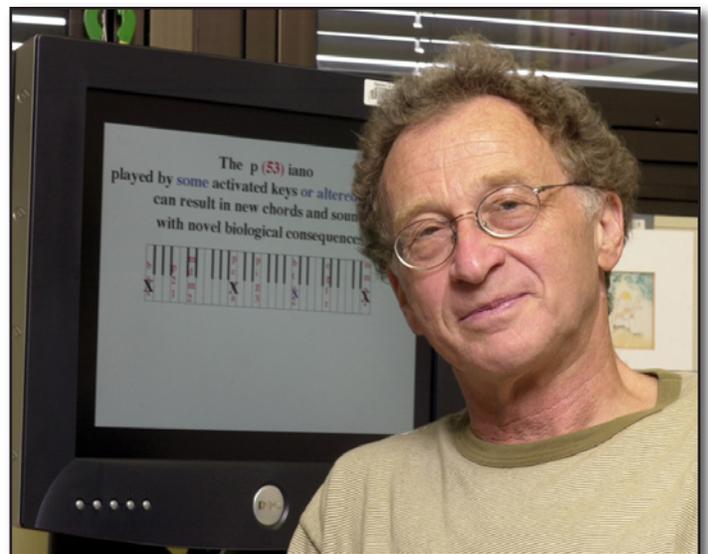
*By Robin Arnette*

Researchers offer the first evidence that DNA damage can lead to the regulation of inflammatory responses, the body's reaction to injury. The proteins involved in the regulation help protect the body from infection.

The [study](#), performed by scientists at the National Institute of Environmental Health Sciences (NIEHS), which is part of the National Institutes of Health, is one of the first studies to come out of the recently established [NIEHS Clinical Research Unit \(CRU\)](#).

Appearing in the March 31 issue of PLoS Genetics, the research suggests that an injury to chromosomes alters the expression of a family of genes known as Toll-like receptors (TLRs). TLRs are proteins that play a role in the immune system by defending the body from infection. Following damage, the TLRs interact with the tumor suppressor gene p53 to regulate the amount of inflammation. The NIEHS investigators also establish that the integration of p53 and inflammation only occurs in primates.

Healthy volunteers with informed consent donated their blood cells for the study. The scientists separated white blood cells from the samples and exposed the cells to anticancer agents to activate p53. They then examined the expression of TLR genes. The team detected large variations among individuals, but found that p53 generally



*Mike Resnick (Photo courtesy of Steve McCaw)*

led to the activation of several TLR genes in patients' cells. They also found that TLR activation could be prevented by adding the p53 inhibitor pifithrin.

“We would not have found this connection if we only worked with rat or mice cells,” said [Michael Resnick, Ph.D.](#), principal investigator in the Laboratory of Molecular Genetics (LMG) and corresponding author on the paper. “We needed to have human samples, so our collaboration with the CRU was crucial for these experiments.”

[Stavros Garantziotis, M.D.](#), a principal investigator in the Laboratory of Respiratory Biology (LRB) and the medical director for the CRU, is a co-author on the article. He said that the publication had two main findings: humans evolved an inflammatory response when subjected to DNA damage, and the variation in TLR activity among humans suggests that some people are more prone to inflammation following DNA damage, for example, after receiving cancer therapy.

“Physicians don't have this information now, but understanding who would likely benefit from anti-inflammatory treatment after chemotherapy would greatly increase a doctor's ability to help his or her patient in the future,” Garantziotis continued.

As a physician and co-author of the publication, LRB principal investigator [Michael Fessler, M.D.](#), went a step further in his explanation of how stimulating the human immune system could treat infection, and autoimmune and environmental diseases.

“The immune system very likely plays a role, not only in all inflammatory diseases that afflict humans, but also in cancer,” Fessler concluded. “Because of the new connection discussed in our paper, we may have a new means to manipulate the responses that affect those diseases.”

Now, the researchers are taking advantage of another NIEHS translational program, the [Environmental Polymorphisms Registry \(EPR\)](#), an ongoing study to collect DNA samples from nearly 20,000 North Carolinians. The EPR study will allow scientists to look for genes linked to disease. The study is a collaborative effort between NIEHS and the General Clinical Research Center at the University of North Carolina at Chapel Hill.

Staff Scientist Daniel Menendez, Ph.D., and Visiting Fellow Maria Shatz, Ph.D., are two LMG scientists in the [Chromosome Stability Group](#) who share first authorship on the paper. Menendez added that the EPR work will permit researchers to further examine the association between p53 and inflammation. “In related studies,



*Stavros Garantziotis (Photo courtesy of Steve McCaw)*



*Stavros Garantziotis (Photo courtesy of Steve McCaw)*



*Daniel Menendez (Photo courtesy of Steve McCaw)*

we are looking at individuals who have genetic alterations in the way they might respond to p53 activation,” he said. “We will try to determine if their cells behave differently, and if these subjects have changes in their inflammatory response, or an increased risk for certain inflammatory diseases.”

Citation: [Menendez D\\*](#), [Shatz M\\*](#), [Azzam K](#), [Garantziotis S](#), [Fessler MB](#), [Resnick MA](#). 2011. The Toll-like receptor gene family is integrated into human DNA damage and p53 networks. *PLoS Genet* 7(3): e1001360; doi:10.1371/journal.pgen.1001360 [Online 31 March 2011]. (\*co-first authors)

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*Maria Schatz (Photo courtesy of Steve McCaw)*

## Jetten to investigate a novel stem cell treatment for diabetes

*By Eddy Ball*

NIH announced Feb. 25 supplemental support of \$86,000 in fiscal year 2011 for an innovative research project headed by NIEHS cell biologist Anton Jetten, Ph.D. The award of NIH Common Fund money through the new [NIH Center for Regenerative Medicine \(NCRM\)](#) will support investigation into the role of transcriptional regulator Gli-similar (Glis) 1-3 proteins in the generation of pancreatic beta cells from induced pluripotent stem (iPS) cells, as part of the development of an innovative therapy for the treatment of patients with diabetes.

As Jetten’s proposal explains, the prevention and effective treatment of diabetes is a major public health priority. Currently, 10 percent of U.S. adults have diabetes at an estimated annual cost of \$174 billion, with the incidence expected to rise to as high as 33 percent of the adult population by 2050.

Although state-of-the-art insulin therapy can save lives and benefit patients with adult-onset diabetes, the therapy does not prevent long-term complications. Diabetes can lead to adult blindness, kidney failure, and limb amputation, or to related conditions, cardiovascular disease and stroke, which are chronic diseases that are also on the rise.

### Targeting repression and transcription of genes involved in insulin production

[Jetten](#), who serves as the chief of the NIEHS Laboratory of Respiratory Biology (LRB) and principal investigator of the LRB Cell Biology Group, is building on prior research with Glis3 knockout mice. In those experiments, he and his group found that null mice lack pancreatic beta cells, the natural source of insulin, and develop neonatal diabetes, hypothyroidism, and polycystic kidney disease over the course of their lives.



*Jetten’s research has been focusing on the study of several nuclear proteins, including retinoic acid orphan receptors (RORs). Investigations of the role of RORs led him into the discovery of Glis proteins and their role in diabetes and kidney disease. (Photo courtesy of Steve McCaw)*

Glis and Gli proteins bind specific DNA elements—known as Gli-response elements (GRE)—in the promoter of target genes and can function as activators or repressors of transcription. Studies performed by the Cell Biology Group have demonstrated that Glis genes are expressed in a temporal and spatial manner during development, suggesting that they are important in the regulation of several developmental processes.

As Jetten noted in his proposal, “Genetic studies [have also] linked mutations within the Glis3 gene to increased susceptibility to type 1 and type 2 diabetes in humans,” paralleling findings in animals on the critical importance of Glis3 in diabetes. “Glis3,” Jetten explained, “has a dual role in regulating both the development and maintenance of mature beta cells.”

### Investigating a potential stem cell therapy for diabetes

Jetten pointed to new technologies for reprogramming adult cells to an induced pluripotent state for generating iPS cells from an individual’s readily accessible skin or blood cells. Reprogramming adult cells into insulin-producing beta cells offers an alternative to human embryonic stem cell approaches, and it also eliminates the need for immunosuppressive therapies.

The proposal outlines an elegant series of experiments to test protocols for inducing differentiation in iPS cells, and to determine whether Glis3 might provide a new target for managing diabetes in a therapy designed to produce cells capable of maintaining near-normal regulation of blood sugar.

NCRM is serving as a stem cell resource for the research community. As part of its award, the Center will perform an interim review of Jetten’s project to determine continued funding for fiscal year 2012.

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## Pollution leads to rapid evolution in some fish species

By Robin Arnette

New research funded by the NIEHS [Superfund Research Program \(SRP\)](#) demonstrates that a population of Atlantic tomcod (*Microgadus tomcod*) living in the Hudson River has rapidly evolved resistance to polychlorinated biphenyls (PCBs), man-made industrial chemicals known to cause cancer in animals. The published work appeared in the Feb. 17 online issue of *Science* magazine and represents the first study to identify the mechanism of resistance to toxicants in any vertebrate population, and the first to show that PCBs in the Hudson River have caused significant ecological change.

The [study](#) was a collaborative effort by several researchers, including [Isaac Wirgin, Ph.D.](#), and [Mark Hahn, Ph.D.](#), two SRP scientists who have been studying animal adaptability to environmental stress for more than a decade. Their research team found that in Hudson River tomcod, the aryl hydrocarbon receptor 2 (AHR2) gene, responsible for mediating the toxicity of chemical contaminants, contained two variants.



*Wirgin explained that General Electric released approximately 1.3 million pounds of PCBs into the Hudson River from 1947 to 1976. Exposure to these pollutants and strong natural selection probably led to a rapid increase in the frequency of the standing AHR2 variant allele in the Hudson River population. (Photo courtesy of Gordon Cook)* 36

One of these variants lacked two amino acids, which caused a structural change within the AHR2 receptor. The deletion made the fish 100-fold less sensitive to PCBs and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), the most toxic of the polychlorinated dibenzo-p-dioxins/furans (PCDD/Fs). Wirgin said that the research addressed the long-term debate over the number of genes required and the time needed to spur dramatic evolutionary change.

“In this case, resistance to toxicants can occur much more rapidly than previously thought and be due to a [small] change within a single gene,” said Wirgin, an associate professor in the Department of Environmental Medicine at New York University School of Medicine, Tuxedo, N.Y., and lead author on the paper.

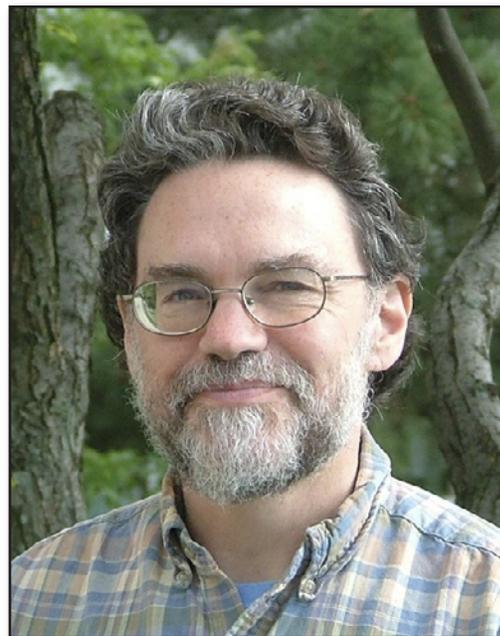
### The consequences of resistance

Hahn, whose SRP sponsorship comes from Boston University, is a senior scientist in the Biology Department at the Woods Hole Oceanographic Institution, Woods Hole, Mass. He said that the AHR2 change and subsequent resistance to PCBs and TCDD isn't found in tomcod from cleaner waters. Hahn also pointed out that although the mutation allowed tomcod to continue to live in the Hudson River, it didn't come without biological consequences.

“One cost is that the fish can accumulate higher levels of PCBs and pass them up the food chain, possibly harming higher-level consumers,” he noted.

“Other potential costs might include altered sensitivity of these fish to additional stressors in their environment, such as other chemicals or severe depletion of oxygen in the water known as hypoxia.”

In addition to his work with tomcod, Hahn studies another fish species known to experience similar evolutionary pressures — the Atlantic killifish (*Fundulus heteroclitus*). The much smaller killifish are like tomcod in that they live in various locations on the U.S. east coast in moderate-to-high levels of chemical contamination. Even though the same gene, AHR2, is experiencing evolutionary selection in these killifish, Hahn's work has identified 26 different AHR2 variants, as opposed to just two in tomcod.



*Hahn stressed that not all animal populations living under selective pressure from contaminants will evolve resistance like these fish. “Tomcod and killifish happen to have life-history characteristics, such as genetic variability, large population size, and short generation time, which allow them to adapt,” he said. (Photo courtesy of Hahn’s wife, Rachel Graber)*

### Atlantic tomcod resistance to toxins in the news

Since its publication, the results of the research have been mentioned in several news media outlets. A few are listed below.

- NIEHS SRP Research Brief 195 – Mechanism of resistance to PCB toxicity in fish [http://tools.niehs.nih.gov/srp/researchbriefs/view.cfm?Brief\\_ID=195](http://tools.niehs.nih.gov/srp/researchbriefs/view.cfm?Brief_ID=195)
- NIEHS SRP What's New Web page – SRP researchers pinpoint “rapid evolutionary change” in Atlantic tomcod <http://www.niehs.nih.gov/research/supported/srp/news/#WirginHahn>
- NIEHS Environmental Factor Extramural Paper – Rapid evolution of Hudson River tomcod <http://www.niehs.nih.gov/news/newsletter/2011/march/science-extramural/#one>
- Science News Podcast  [http://podcasts.aaas.org/science\\_podcast/SciencePodcast\\_110218.mp3](http://podcasts.aaas.org/science_podcast/SciencePodcast_110218.mp3)
- NPR All Things Considered – Toxic avengers: pollution drove fish evolution  <http://www.npr.org/2011/02/17/133842089/toxic-avengers-pollution-drove-fish-evolution>

## SRP pushes environmental research forward

[Richard Di Giulio, Ph.D.](#), although not an author on this paper, has also studied chemical resistance in the killifish, but in the Elizabeth River in North Carolina. Di Giulio is a professor of environmental toxicology and director of the SRP Center and Integrated Toxicology Program at Duke University in Durham, N.C. He said his work and the work of others “not only shows the remarkable ability of resident fish populations to adapt to toxicity, but could also be applied to other aquatic and estuarine systems that are chronically polluted.”

Bill Suk, Ph.D., director of the [Center for Risk and Integrated Sciences \(CRIS\)](#), the center within the NIEHS Division of Extramural Research & Training (DERT) that manages the SRP, said he was happy that SRP played a role in this research because it is a great example of one of the goals of NIEHS.

“This work enforces the link between resistance and susceptibility and shows how important basic mechanistic research is in addressing a problem,” Suk concluded.

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

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## Infertility linked to PCB exposure

*By Angelika Zaremba*

In an NIH-funded study published in February, investigators report that polychlorinated biphenyls (PCBs), in concentrations representative among the general U.S. population, were associated with failed embryo implantations in women undergoing *in vitro* fertilization (IVF). Although PCB production was banned in the U.S. and other developed countries more than 30 years ago, they were used extensively and persist in the environment, making exposure a significant public health issue even today.

As far as they are aware, the researchers believe this [investigation](#) represents the first use of IVF to explore the association of PCBs and chlorinated pesticides with infertility and early pregnancy loss. “This study population,” they write, “serves as a unique model to study early pregnancy endpoints that are not otherwise observable in women conceiving naturally.”

The team of scientists was led by [John Meeker, Sc.D.](#), first and corresponding author, and [Russ Hauser, M.D., Sc.D.](#), principal investigator. Meeker is an assistant professor at the University of Michigan School of Public Health, and Hauser is the Frederick Lee Hisaw Professor of Reproductive Physiology at the Harvard School of Public Health. The study was conducted in collaboration with Daniel Cramer, M.D., Sc.D., and Stacey Missmer, Sc.D., of Brigham and Women’s Hospital in Boston.



*Meeker is also the principal investigator on an NIEHS [grant](#) to research bisphenol A and phthalate exposure in relation to fetal growth and preterm birth. (Photo courtesy of John Meeker)*

## PCBs in the environment

The general population is exposed to PCBs primarily through ingestion of contaminated food, such as fish, meat, and dairy products, but also through occupational, ambient, and indoor sources. The half-life of PCBs in the blood ranges from one to more than ten years. Exposure to PCBs has been associated with a range of adverse health effects, including adverse effects on reproduction and increased risk of pregnancy loss.

Animal studies have demonstrated associations between PCB exposure and endometriosis and altered menstrual cycles. Exposure impairs oocyte maturation and adversely affects blastocyst formation and embryo development.

## Consistent with earlier findings

Analysis of serum samples of 765 women, with a mean age of 36, undergoing 827 *in vitro* fertilization cycles between the years 1994 and 2003 showed dose-dependent trends of PCBs with increased odds of failed implantation and reduced live births. Three PCB congeners — PCBs 118, 138, and 153 — were analyzed in relationship to IVF outcome, individually and in sum.

PCB 153 individually showed the strongest association with IVF outcome. The odds of failed implantations were doubled and the odds of live birth were reduced by 41% among women with the highest concentrations of PCB 153, compared to women with the lowest concentrations.

The authors explain that their results are consistent with epidemiological studies of PCB exposure and time to pregnancy (TTP), an endpoint that lacks specificity since it may represent one or more aspects of male or female reproductive health.

## Looking to the future

Although this prospective study gains strength from its large sample size, and examination of exposure biomarkers and outcome measures collected at or near the likely time window of interest, the researchers acknowledge that it has some limitations.

Oocyte qualities were not included, nor were serum PCB levels of male partners. Reductions in semen quality have been reported in relation to PCB exposure, which may also contribute to the success of IVF. As with nearly all environmental epidemiologic studies, there remain questions of causality and confounding co-exposures. In addition, the generalizability of findings for women undergoing IVF to wider populations is unknown.

The etiology of infertility and early pregnancy loss remains largely unexplained. The results from this study will help to understand and identify potential environmental risk factors for this important public health challenge. “These findings may help explain previous reports of reduced fecundability and increased TTP among women exposed to PCBs,” the researchers conclude.

The study was funded by an NIEHS [grant](#) and by a grant from the Eunice Kennedy Shriver National Institute of Child Health and Human Development.



*Hauser is principal investigator on an additional three NIEHS grants on the effects of environmental exposures on fertility and development, as well as children's health. (Photo courtesy of Russ Hauser)*

*Citation:* Meeker JD, Maity A, Missmer SA, Williams PL, Mahalingaiah S, Ehrlich S, Berry KF, Altshul L, Perry MJ, Cramer DW, Hauser R. 2011. Serum concentrations of polychlorinated biphenyls (PCBs) in relation to *in vitro* fertilization (IVF) outcomes. *Environ Health Perspect*; doi:10.1289/ehp.1002922 [Online 24 Feb 2011].

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

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## New hope in the treatment of cystic fibrosis

By Ed Kang

NIEHS-funded scientists recently unveiled the discovery of a potential therapeutic that could dramatically transform the treatment of cystic fibrosis, chronic obstructive pulmonary disease (COPD), and other related lung diseases.

At the March 22 installment of the NIEHS Keystone Seminar Series, Dan Baden, Ph.D., of the University of North Carolina Wilmington (UNCW), chronicled his research that began as an investigation into toxicological mechanisms and has led to the creation of a product with tremendous promise.

### The flipside of red tide's toxicological effects

Baden, who has a long-standing relationship with NIEHS, and his team of researchers at the UNCW Center for Marine Science are doing what few, if any, NIEHS researchers have before – parlaying the study of an environmental toxicant into the development of a novel treatment for disease.

Under a grant from NIEHS, Baden has been investigating the toxicological effects of Florida red tide, or *Karenia brevis*. This extremely toxic microorganism blooms off the coast of Florida annually. It causes fish and marine mammals to die, and when aerosolized by the wind and tide, causes people, even miles inland, to cough, sneeze, and experience other respiratory symptoms.

“Airborne materials from the red tide can cause severe bronchoconstriction at extremely low concentrations measured in only a few trillionths of a gram per cubic meter of air,” says Baden.

Trying to uncover the toxic mechanisms for these inhaled particles, Baden's lab has developed the largest *Karenia brevis* cultivation facility in the country, where they extract component fractions for bioactive materials.

The power of one of those components, brevenal, was discovered when looking for toxicological effects of *Karenia brevis* in fish bioassays.



*“NIEHS has always been very supportive, and we're now at a point where we're going to start giving back,” said Baden. “The molecules that we're producing now could treat a multitude of diseases.”*  
(Photo courtesy of Steve McCaw)



*Fred Tyson, Ph.D., of the Cellular, Organ, and Systems Pathobiology Branch, was the host for the seminar and is the program administrator for Baden's current grant. Tyson noted, “Dan's relationship with NIEHS goes back to his graduate student days.”* (Photo courtesy of Steve McCaw)

Lead toxicologist and marine biologist Andrea Bourdelais, Ph.D., observed that some fish weren't dying, despite multiple exposures.

That left her with the hypothesis that the scientists were either working with a fish that was less sensitive to toxic materials or they had uncovered an antitoxin. Within weeks, a subsequent experiment in sheep confirmed that the bronchoconstriction caused by the toxin could be prevented, reduced, or reversed by the antitoxin brevenal at extremely low concentrations.

"The interesting thing is that the toxin and the antitoxin are both produced by the same organism but in different amounts and at different times in the cell cycle," remarks Baden.

### **From toxic tide to the medicine cabinet**

The antitoxin creates a thinner mucous-promoting accelerated removal of particles from the lungs. "Brevenal is effective at a million-fold lower concentration than other therapeutic agents," says Baden. "With brevenal, you can actually turn the bronchial constriction off very efficiently."

Baden is embarking on a licensing agreement with a major pharmaceutical firm, and with financial assistance from an NIEHS Recovery Act grant, is hoping to finish preclinical work in 90 days, then move on to clinical trials.

"When a discovery like this is made initially, the hardest thing to deal with are the parents of children with the disease asking when they can get the drug for their child," Baden explained. "That bolsters our need to work faster and do better work to get it to the clinical realm."

But with a new therapeutic target and remarkably high potency, Baden's team's serendipitous discovery could ultimately be a blockbuster drug for those suffering with certain forms of respiratory illness.

(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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## **Thomas explores advances in risk assessment using genomics**

*By Mamta Behl*

Russell Thomas, Ph.D., director of the Center for Genomic Biology and Bioinformatics and a senior investigator at The Hamner Institutes for Health Sciences, presented a talk at NIEHS March 21 on the application of non-traditional approaches to risk assessment, as part of the NTP Biomolecular Screening Branch (BSB) seminar series.

In his talk, titled "Application of Transcriptional Benchmark Dose Values in Quantitative Cancer and Noncancer Risk Assessment," [Thomas](#) explored the current status of risk assessment and the potential for incorporating genomic technology into an emerging paradigm of predictive toxicology. He began his survey with a review of several of the issues being addressed by the [Tox21](#) consortium



*NTP Host Susceptibility Branch Molecular Toxicologist [Scott Auerbach, Ph.D.](#), hosted Thomas' presentation as part of the BSB seminar series and fielded the questions that followed. (Photo courtesy of Steve McCaw)*

made up of the NTP, NIH Chemical Genomics Center (NCGC), U.S. Environmental Protection Agency (EPA), and its most recent partner, the U.S. Food and Drug Administration (FDA).

### Current status of risk assessment

One of the current challenges in risk assessment is that “chemicals without published reference values are not considered quantitatively in the overall hazard index calculation when evaluating contaminated sites where multiple chemicals exist,” explained Thomas. He pointed to some limitations of the existing risk assessment paradigm, such as the cost, time, and number of animals used in the traditional toxicity tests that support a risk assessment. As a result, a vast number of chemicals are largely ignored when risk assessment is performed at Superfund sites, and potentially harmful ones can be interpreted as posing no risk to human health, he continued.

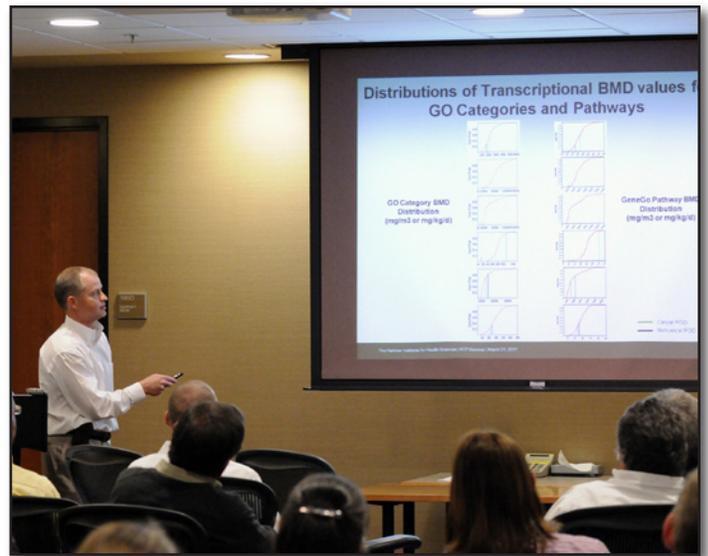
### Incorporation of genomic technology in risk assessment

In explaining why genomics may offer a useful approach for filling the data void, Thomas said that the use of genomic technology in toxicology began more than a decade ago and since then has transitioned from being a specialized laboratory technique to an off-the-shelf commodity. Current genomic technology now includes the capability to survey the entire transcriptome.

As Thomas explained, “The technology has become more reliable and reproducible.” Hence, he sees the primary advantages of applying genomic technology to risk assessment as “being able to sensitively and comprehensively examine the molecular changes resulting from chemical exposure.” An important application of this technology lies in providing both quantitative and qualitative information on the dose at which cellular processes are transcriptionally affected in what Thomas referred to as “a transcriptional point of departure for chemical risk assessment” (see text box).

### A lively discussion

In addressing such questions as whether we know which transcriptional markers are correlated with specific pathological endpoints and how tissue-specific non-cancer endpoints can be assessed, Thomas responded that even though different chemicals may act by different mechanisms to elicit these pathological endpoints, common processes or pathways that are transcriptionally altered, which are what he called “bioindicators of



*In the course of his talk, Thomas maintained, “The degree of correlation between the transcriptional BMD values and those for the traditional apical endpoints suggests that they may be used as potential surrogates for both cancer and non-cancer points of departure.” (Photo courtesy of Steve McCaw)*



*Among the many attendees who asked questions in the course of the extended question and answer session was SRA contractor Ruchir Shah, Ph.D., a specialist in genomics and bioinformatics. (Photo courtesy of Steve McCaw)*

effect,” can still be identified, even though they may be independent of the mechanism. He went on to describe possible ways this technology may be applied to chemicals with unknown effects or target organs.

(Mamta Behl, Ph.D., is a research fellow in the NTP Toxicology Branch)



*Thomas left the roomful of scientists with an appreciation for the potential of bringing about a change in the established methodology of risk assessment and stimulated an animated discussion of questions that remain to be answered. (Photo courtesy of Steve McCaw)*

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## Transitioning from traditional end points to newer metrics of biological perturbation

Thomas explained that a risk assessment for non-cancer and cancer endpoints is usually conducted using dose response modeling approaches where a dose is identified that causes a defined increase in an adverse effect.

“The dose response modeling approaches are referred to as benchmark dose analysis, and a benchmark dose (BMD) can be thought of as a transition point between a no observed adverse effect level (NOAEL) and a lowest observed adverse effect level (LOAEL) within a dose-response curve,” said Thomas. Referring to his recent [study](#) on the topic, he explained how BMD values are calculated for cancer and non-cancer endpoints and provided examples of the way BMD methods have been applied to previous NTP studies for both cancer and non-cancer endpoints.

Thomas described a method his group has developed that allows for transcriptomic data to be used for calculating genomic-based BMD values for individual genes and sets of genes with shared biological roles (referred to as gene ontologies). He showed how the most sensitive BMD values derived from liver and lung transcriptomic measurements following a subchronic exposure were slightly more sensitive than BMD values for traditional cancer and non-cancer apical endpoints.

Thomas explained that this comparison demonstrates, counter to common belief, that transcriptome changes at 90 days are not orders of magnitude more sensitive than apical toxicity endpoints. He went on to show that the genomic BMDs for gene ontologies related to stress signaling and inflammatory processes correlate strongly with BMDs for cancer and non-cancer apical endpoints, respectively. Finally, he outlined an approach by which genomic-based BMDs may be incorporated into chemical risk assessment.

*Citation:* [Thomas RS, Clewell HJ 3rd, Allen BC, Wesselkamper SC, Wang NC, Lambert JC, Hess-Wilson JK, Zhao QJ, Andersen ME. 2011. Application of transcriptional benchmark dose values in quantitative cancer and noncancer risk assessment Toxicol Sci 120\(1\):194-205.](#)

# Agreement increases international cooperation to reduce animal testing

By NICEATM

NIEHS/NTP Director Linda Birnbaum, Ph.D., joined international counterparts March 8 in Washington, D.C., to sign an agreement that will expand international efforts to reduce the number of animals required for chemical safety testing. The agreement brings a new country, the Republic of Korea, into an existing effort to promote international cooperation that should permit more rapid acceptance of new safety testing methods for chemicals and products. New testing methods can better protect public health and also reduce the number of animals needed for safety testing.

The agreement, known as the International Cooperation on Alternative Test Methods (ICATM), was signed in a ceremony during the 50th Annual Meeting of the Society of Toxicology. Birnbaum signed as the U.S. representative on behalf of the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), one of the national organizations participating in the agreement.



*Seung Hee Kim, Ph.D., director general for the National Institute of Food and Drug Safety Evaluation at the Korea Food and Drug Administration, addressed the audience gathered for the signing ceremony. (Photo courtesy of NICEATM)*

## Uniting scientists in Europe, North America, and Asia

The updated agreement expands the original ICATM memorandum of cooperation signed in April 2009 ([see story](#)). The agreement was also signed by representatives from participating validation organizations within the European Union, Canada, Japan, and Korea.

In remarks welcoming the participants to the signing ceremony, Birnbaum highlighted the successes that have already been realized during the first two years of the agreement, and looked forward to future successes that will include input from Korean scientists. Representatives of the participating national validation organizations also made brief statements, as did NICEATM Director Rear Adm. William Stokes, D.V.M., and Jodie Kulpa-Eddy, D.V.M., chair of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), which is administered by NICEATM.

There is a growing international need for new test methods that better predict the safety or hazards of chemicals and chemical products. U.S. and international laws also require that new methods used for research and testing reduce, refine to decrease or eliminate pain and distress, or replace animal use to the greatest extent possible.

The ICATM agreement will promote international cooperation on the scientific validation of these new test methods. Test methods that are shown to be reproducible and accurate based on strong scientific information will be more readily accepted by regulatory agencies worldwide. This will, in turn, lead to their broader acceptance and use, benefitting both public health and animal welfare. Worldwide acceptance of test methods also benefits economic development, by allowing manufacturers to satisfy testing requirements in many international markets with a single safety test.

More information on the ICATM agreement is available on the NICEATM-ICCVAM [Web site](#).



*Signatories, seated left to right, are Birnbaum; Inskip; Kreysa; Yasuo Ohno, Ph.D., from the National Institute of Health Sciences in Japan; and Kim. Standing, left to right, are Kulpa-Eddy; Stokes; Kojima; Han; Soojung Sohn, Ph.D., from KoCVAM; and Bong Hyun Nam, Ph.D., from the Embassy of the Republic of Korea. (Photo courtesy of NICEATM)*

## **NICEATM director chairs SOT session on ICATM**

Stokes co-chaired a session on ICATM at the recent annual meeting of the Society of Toxicology (SOT). The goal of the session was to inform SOT attendees of the important role ICATM plays in facilitating the rapid international adoption of new validated alternative safety testing methods.

In addition to chairing the session, titled “The International Cooperation on Alternative Test Methods (ICATM): Translating Science to Provide Improved Public Health Safety Assessment Tools,” Stokes gave an introductory presentation that described the purposes and goals of ICATM. His presentation also outlined the validation process for new test methods and noted the positive impact that the ICATM agreement had on the adoption of international guidelines for chemical safety testing in 2009 and 2010.

Also co-chairing the session was Marilyn Wind, Ph.D., who presented a summary of ICATM contributions by NICEATM and ICCVAM. Wind, who recently retired from the U.S. Consumer Product Safety Commission, was ICCVAM Chair from 2007 to 2010 and was instrumental in developing the original ICATM agreement signed in 2009.

Following Stokes’ and Wind’s talks, representatives of the other national validation organizations that participate in ICATM gave presentations summarizing their organizations’ contributions and roles in ICATM, as well as future plans. Presenters included Joachim Kreysa, Ph.D., for the European Centre for the Validation of Alternative Methods (ECVAM); Hajime Kojima, Ph.D., for the Japanese Center for the Validation of Alternative Methods (JaCVAM); Mike Inskip for the Environmental Health Science and Research Bureau of Health Canada; and Soon Young Han, Ph.D., for the Korean Center for the Validation of Alternative Methods (KoCVAM).

Presentations from the ICATM session, as well as other NICEATM-ICCVAM presentations at the 2011 SOT Annual Meeting, are available on the NICEATM-ICCVAM [Web site](#).

# This month in EHP

By Matt Goad

Public health officials are starting to speak out about what they see as a lack of preparation for managing the human health issues expected to arise from climate change. Now public health departments are evaluating how to develop climate change adaptation policies at the local and state level, in a move beyond simple mitigation efforts. The April issue of [Environmental Health Perspectives \(EHP\)](#) takes a look at this shift in its feature article, “Preparing a People: Climate Change in Public Health.”

April’s second news story, “Black Carbon: The Dark Horse of Climate Change Drivers,” looks at the latest climate science on black carbon, considered by many experts to be the best candidate for high-impact emission-reduction policies, and discusses where policy on this pollutant, the major component of diesel exhaust, might head in the future.

In the [podcast](#) for the month, Richard Lemen, Ph.D., former U.S. assistant surgeon general and deputy director of the National Institute for Occupational Safety and Health, tells host Ashley Ahearn what’s driving worldwide trends in asbestos use.

Among the reviews and research included in this issue of EHP are:

- PM-Induced Health Effects: Who Is Susceptible?
- Formaldehyde Alters Lung Cell microRNA Expression
- Comparison of BPA Kinetics in Mice, Monkeys, and Humans
- Global Magnitude of Reported and Unreported Mesothelioma

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

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## Upcoming distinguished lecturer Ron de Kloet

By Eddy Ball

The 2010-2011 NIEHS Distinguished Lecture Series continues a series of talks on neuroscience when it hosts a lecture by neuroendocrinologist Ron de Kloet, Ph.D., April 12. De Kloet will discuss his research into stress, hormones, and the brain in a presentation titled “Resilience or vulnerability to environmental challenge? A question of stress, genes and balance.”

Honored as academy professor by the Royal Netherlands Academy of Arts and Sciences, [de Kloet](#) is a professor in the Department of Medical Pharmacology and former head of the Division of Medical Pharmacology at



<http://twitter.com/ehponline>



Leiden University. He is a prolific researcher, having authored or co-authored 462 articles in peer-review journals, 131 reviews, and six books.

In 2010, de Kloet was honored for his career achievements as a knight of the Order of the Dutch Lion during the [7th World Congress on Stress](#) in Leiden — the latest in a long list of awards for his contributions to neuroendocrinology and psychiatry. He is a member of several major professional societies and serves as the chairman of the Scientific Advisory Board for the Max Planck Institute for Psychiatry.

De Kloet studies the effects of chronic stress and elevated or reduced cortisol on feedback loops in neuronal circuits that underlie emotional and cognitive functioning. The overall objective of his research program is to identify the cortisol -dependent mechanism underlying the pathogenesis of severe depression.

His lab at the Leiden/Amsterdam Center for Drug Research employs genomics, systems biology, and bio-informatics approaches in animal models and in the post-mortem material of patients to identify patterns of responsive gene/protein products. Candidate genes are then manipulated in animal models to address the questions of how cortisol can impair cognition and emotion, as well as how anti-glucocorticoids ameliorate the impaired cognitive and emotional processes, using behavioral, endocrine, and imaging endpoints.

The talk, which begins at 11:00 a.m. in Rodbell auditorium will be hosted by NIEHS Molecular Endocrinology Group Principal Investigator and Chief of the Laboratory of Signal Transduction [John Cidlowski, Ph.D.](#)

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## Upcoming distinguished lecturer Edison Liu

*By Eddy Ball*

The 2010-2011 NIEHS Distinguished Lecture Series shifts gears on April 22 when it hosts geneticist Edison Liu, M.D., for a talk on “Systems Biology in Cancer Medicine: Harnessing Complexity” ([see text box](#)).

Liu is the executive director of the [Genome Institute of Singapore](#), an international research institute focused on integrating genomic sciences with cell and medical biology. He also serves as the president of the [Human Genome Organisation \(HUGO\)](#) and holds several academic appointments in Singapore and the U.S.

Liu received his B.S. and M.D. degrees from Stanford University, followed by training at both Stanford and the University of California, San Francisco. This was followed by his nine-year career at the University of



*After completing his postdoctoral training at Rockefeller University in 1975, de Kloet returned to the Netherlands to teach at the University of Utrecht before accepting his current position at Leiden University. Reflecting on his nearly four decades of research, he opened the multidisciplinary 7th World Congress on Stress last summer with a plenary lecture outlining his vision of “The Future of Stress.” (Photo courtesy of Ron de Kloet)*



**Linked video:**

[Liu describes the power of a systems biology approach to studying cancer during an interview at the National Cancer Research Institute Cancer Conference in November 2010 \(07:59\)](#)

(Launches in new window)

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North Carolina at Chapel Hill, where Liu developed leukemia and breast cancer research programs, directed the Specialized Program of Research Excellence (SPORE) in Breast Cancer, led the Breast Cancer Program at the Lineberger Comprehensive Cancer Center, and served as chief of the Division of Medical Genetics at the School of Medicine. Liu then moved to the National Cancer Institute, where he served as the scientific director of the Division of Clinical Sciences before moving to his current position at the Genome Institute of Singapore.

Liu describes his work as spanning cancer biology, genomics, human genetics, and molecular epidemiology. Recognized as a top breast cancer researcher, he was a pioneer in investigating the roles of AXL and HER2/ErbB-2 in human breast cancers, and identifying these genes, as well as others, as potential targets for therapeutic intervention. Liu's recent work centers on the functional genomics and genetics of human cancers utilizing genome-wide systems approaches in deciphering critical signaling pathways.

The talk, which begins at 11:00 a.m. in Rodbell Auditorium, will be hosted by NIEHS Environmental Stress and Cancer Group Principal Investigator [Rick Paules, Ph.D.](#), who also serves as the director of the Microarrays Core Facility and acting chief of the Laboratory of Toxicology and Pharmacology.



*Liu has received many awards, including the Brinker International Award and the Rosenthal Award from the American Association for Cancer Research. He is executive editor of the journal [Breast Disease](#) and is a member of several major cancer-related professional societies. (Photo courtesy of Edison Liu)*

## **Liu's abstract – Systems biology in cancer medicine: Harnessing complexity**

Genomic medicine involves the provision of medical care that uses the power of genomic knowledge and technologies to resolve complex problems. The fundamental difference between this and older strategies in medicine research is the comprehensiveness and the precision of the analyses afforded by new genomic technologies such as in sequencing, cloning, and genotyping. The new challenge will be the assembly and management of this high volume of data with dimensional complexity. Genomic medicine therefore means computational and systems medicine as well. Systems biology, as a discipline, seeks to explain biologic phenomenon through the net interactions of all cellular and biochemical components within a cell or organism. Operationally, systems biology requires the digitalization of biological output, the computational power to analyze comprehensive and massive datasets, and the capacity to integrate heterogeneous data into a usable knowledge format.

We will describe how genomic approaches are changing our understanding of cancer, as a model system. Our work, at the Genome Institute of Singapore, in transcriptional profiling has led to transcription factor binding site dynamics and human variations in those binding sites. We have moved to study the consequences of structural mutations in cancer genomes. We employ a strategy of using genomic data to reconstruct systems maps of critical regulatory networks. This integrative approach permits modeling of complex interactions and allowed us to quickly uncover complex mechanisms of drug action. Finally, the ability to sequence cancer genomes in a cost effective manner allows for the identification of unique and private mutations for each individual patient's cancer.

# Extramural papers of the month

By Jerry Phelps

- Resveratrol protects mother and fetus from immunotoxic effects of TCDD
- Human-induced pluripotent stem cells exhibit extensive epigenomic reprogramming
- Arsenic exposure may increase mortality from tuberculosis
- Tobacco smoke enhances the progression of diabetic nephropathy



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

## Resveratrol protects mother and fetus from immunotoxic effects of TCDD

A recent study by NIEHS grantees at the University of South Carolina School of Medicine found that administration of resveratrol protects the mother and developing fetus from the immunotoxic effects of dioxin. Resveratrol is a natural product found in grapes, red wine, nuts, berries, and other plants, and is also available as an over-the-counter supplement. It has anti-inflammatory properties and is touted as a natural treatment for autoimmune disorders.

Pregnant laboratory mice were injected once with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) at 10 micrograms per kilogram body weight on gestation day 14. The pregnant mice also received resveratrol at 100 milligrams per kilogram body weight orally from gestation day 14 to 19. The researchers observed that resveratrol protected the pregnant mice and their offspring from dioxin-induced thymic atrophy, apoptosis, and alterations in T-cell receptor expression. It also significantly reduced thymus expression of cytochrome P450-1A1.

These findings demonstrate that, in laboratory animals, administration of resveratrol during pregnancy affords protection to the mother and the fetus from the toxicity induced by environmental pollutants that have their effects through activation of the aryl hydrocarbon receptor. Additional studies are needed before similar claims can be made for humans.

*Citation:* Singh NP, Singh US, Nagarkatti M, Nagarkatti PS. 2011. Resveratrol (3,5,4'-trihydroxystilbene) protects pregnant mother and fetus from the immunotoxic effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Mol Nutr Food Res* 55(2):209-219.

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## Human-induced pluripotent stem cells exhibit extensive epigenomic reprogramming

Reprogramming adult cells to regain their ability to differentiate into a variety of cells appears to leave indelible marks, report NIEHS-supported researchers. When the team scoured the epigenomes of induced pluripotent stem (iPS) cells, they found a consistent pattern of reprogramming errors. What's more, these incompletely reprogrammed hotspots were maintained when iPS cells were differentiated into a more specialized cell type,

providing an iPS cell-specific signature, enabling the researchers to determine whether a cell was an iPS or an embryonic stem cell, simply by examining these hotspots.

Reprogramming induces a complete reconfiguration of the DNA methylation pattern throughout the genome, returning it to an embryonic stem cell-like state. Overall, this process results in an iPS cell methylation pattern very similar to that of embryonic stem cells, but when the team looked further, they discovered significant differences. Their experiments revealed considerable variability between iPS cell lines, including a memory of their tissue of origin. Regardless of their individual history, iPS cells showed a common defect — hotspots near telomeres and centromeres that proved resistant to reprogramming.

These findings confirm that iPS cells, which by all appearances look and act like embryonic stem cells, differ in certain aspects from their embryonic cousins, emphasizing that further research will be necessary before they can be rightful substitutes for embryonic stem cells.

*Citation:* [Lister R, Pelizzola M, Kida YS, Hawkins RD, Nery JR, Hon G, Antosiewicz-Bourget J, O'Malley R, Castanon R, Klugman S, Downes M, Yu R, Stewart R, Ren B, Thomson JA, Evans RM, Ecker JR. 2011. Hotspots of aberrant epigenomic reprogramming in human induced pluripotent stem cells. Nature 471\(7336\):68-73.](#)

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## **Arsenic exposure may increase mortality from tuberculosis**

According to scientists supported by NIEHS and the Superfund Research Program, increased mortality from pulmonary tuberculosis could be yet another serious outcome from exposure to arsenic in drinking water. These findings are from an ongoing study in Chile and, if confirmed in other arsenic-exposed populations, they will have important public health implications, since some of the largest arsenic-exposed populations are in developing countries with widespread tuberculosis.

Tuberculosis is a major public health problem worldwide, causing over 2 million deaths in the last year alone and 9 million new infections. Increased susceptibility to tuberculosis has been identified with a variety of other diseases and exposures. Likewise, arsenic in drinking water is a serious public health problem affecting many countries, with millions of people throughout the world exposed.

The findings constitute the first evidence relating arsenic exposure to tuberculosis. The researchers compared mortality rate ratios with time patterns of arsenic exposure, which increased abruptly in 1958 in a specific region in Chile and then started declining in 1971. Tuberculosis mortality rate ratios in men started increasing in 1968, 10 years after high arsenic exposure commenced. The peak male 5-year mortality rate ratio occurred during 1982-1986. The findings are biologically plausible in view of evidence that arsenic is an immunosuppressant and also a cause of chronic lung disease.

*Citation:* [Smith AH, Marshall G, Yuan Y, Liaw J, Ferreccio C, Steinmaus C. 2011. Evidence from Chile that arsenic in drinking water may increase mortality from pulmonary tuberculosis. Am J Epidemiol 173\(4\):414-420.](#)

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# Tobacco smoke enhances the progression of diabetic nephropathy

Using a diabetic mouse model, researchers from the University of Alabama at Birmingham report that exposure to tobacco smoke worsens the progression of diabetic nephropathy, likely mediated by increased expression of profibrotic cytokines.

Diabetic nephropathy is the most common cause of end-stage renal disease in the U.S. It is characterized by proteinuria and irreversible changes, such as sclerosis, in the structure and function of the glomeruli, the filtering structures in the kidney. These changes effectively reduce the kidney's ability to filter waste and toxins from the blood by reducing the glomerular filtration surface. Cigarette smoking is now recognized as a risk factor in the progression of chronic kidney disease.

In the current study, the mice were exposed to tobacco smoke for eight weeks at roughly the same levels as those found in active smokers. Tobacco smoke exposure caused significant increases in mesangial expansion, accompanied by increases in expression of transforming growth factor beta and fibronectin, as compared to the control group mice that breathed regular air.

These studies demonstrate that smoking and exposure to environmental tobacco smoke may further the progression of diabetic nephropathy. The researchers conclude, based on this and previous research, that nicotine may be mediating these effects.

*Citation: Obert DM, Hua P, Pilkerton ME, Feng W, Jaimes EA. 2011. Environmental tobacco smoke furthers progression of diabetic nephropathy. Am J Med Sci 341(2):126-130.*

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

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## Intramural papers of the month

*By Jeffrey Stumpf and Ritu Rana*

- [SNPs modulate cellular stress response](#)
- [Decreasing DNA binding may reverse mutator phenotype](#)
- [Regulation of metabolic syndrome by the nuclear receptor TAK1/TR4](#)
- [Occupational hazards of agriculture](#)

## SNPs modulate cellular stress response

Researchers from the NIEHS Environmental Genomics Group have identified human single-nucleotide polymorphisms (SNPs) that change the expression of a nearby gene in response to cellular stress. Binding of the p53 tumor suppressor to a specific sequence of DNA, which activates transcription of the target genes, was altered by the SNPs.

Most of 14.5 million human SNPs likely include non-coding SNPs that affect gene expression by altering DNA binding by transcription factors. This study used a bioinformatic approach to narrow the 6538 SNPs in suggested p53 binding sites to 32 likely candidates and validated this approach with a global search using chromatin immunoprecipitation. Binding of p53 to sequences containing these SNPs was directly tested using a microsphere DNA binding assay. Finally, the researchers reported changes in gene expression in human cell lines treated with a known agonist of the p53 response, doxorubicin.

Activation of the cascade of genes under p53 control in response to DNA damaging agents is important for suppression of tumors. Changes in the intensity of the p53 response changes depending on genetic sequence, as seen in this study, may explain different susceptibilities of environmentally induced diseases such as cancer.

*Citation:* [Bandeled OJ, Wang X, Campbell MR, Pittman GS, Bell DA](#). 2011. Human single-nucleotide polymorphisms alter p53 sequence-specific binding at gene regulatory elements. *Nucleic Acids Res* 39(1):178-189.

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## Decreasing DNA binding may reverse mutator phenotype

In a collaborative effort, researchers from NIEHS and the Polish Academy of Sciences reported the strongly antimutagenic impact of an amino acid replacement in the RB69 viral DNA polymerase. The results, published in the *Journal of Molecular Biology*, showed that the powerful mutator phenotype of one amino acid replacement (Tyr567Ala) is reversed when paired with another replacement (Ser565Gly), even though Ser565Gly by itself hardly affects fidelity.

RB69 is a bacteriophage that uses its own DNA polymerase when infecting *E. coli* cells. Good crystal structures of the RB69 polymerase and easily measured replication fidelity make this polymerase ideal for studying basic aspects of how polymerases prevent mutagenesis. The Ser565Gly replacement seems to work both by altering the binding of the polymerase to DNA in a way that promotes the antimutagenic action of DNA proofreading by the same or new polymerase molecule, and by rendering the DNA binding pocket more rigid, and thus more able to reject imperfect base-base mispairs.

Mutagenesis affects many aspects of human health, including genetic diseases, accumulation of drug-resistant bacteria and viruses, and precursors to cancer. Basic research in DNA replication is key to understanding the role of mutagenesis in disease and providing potential targets for pharmaceutical agents.

*Citation:* [Trzemecka A, Jacewicz A, Carver GT, Drake JW, Bebenek A](#). 2011. Reversal of a mutator activity by a nearby fidelity-neutral substitution in the RB69 DNA polymerase binding pocket. *J Mol Biol* 404(5):778-793.

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## Regulation of metabolic syndrome by the nuclear receptor TAK1/TR4

Researchers from NIEHS and the University of Pittsburgh performed a collaborative study on transforming growth factor beta-activated kinase 1 (TAK1)-deficient mice (TAK1<sup>-/-</sup>) to demonstrate that the loss of TAK1, an orphan nuclear receptor, protects mice against age- and high fat diet (HFD)-induced metabolic syndrome. The study indicated that TAK1 plays a critical role in regulating lipid and energy homeostasis and, thus, may provide a novel therapeutic target for obesity and related pathologies.

Researchers generated TAK1<sup>-/-</sup> mice to better understand the role of TAK1 in obesity and associated pathologies. Using histo- and biochemical assays, they found that TAK1<sup>-/-</sup> mice have low hepatic triglycerides and reduced lipid accumulation in adipose tissue. Microarrays of TAK1<sup>-/-</sup> mice livers revealed that the expression of several genes involved in lipid uptake and triglyceride synthesis and storage was greatly decreased. TAK1<sup>-/-</sup> mice were lean and had a higher rate of energy expenditure. Further, the study reported that TAK1<sup>-/-</sup> mice had reduced inflammatory response in white adipose tissues and were resistant to glucose intolerance and insulin insensitivity.

Altogether, the authors suggest that the TAK1-deficiency prevents TAK1<sup>-/-</sup> mice from age- and HFD-induced liver injury, obesity, and related pathologies, such as diabetes. The findings provide a new therapeutic target for obesity-linked diseases.

*Citation:* Kang HS, Okamoto K, Kim YS, Takeda Y, Bortner CD, Dang H, Wada T, Xie W, Yang XP, Liao G, Jetten AM. 2011. Nuclear orphan receptor TAK1/TR4-deficient mice are protected against obesity-linked inflammation, hepatic steatosis, and insulin resistance. *Diabetes* 60(1):177-188.

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## Occupational hazards of agriculture

Although farmers have lower mortality rates when compared to the general population, NIEHS scientists found that farmers continue to be at higher risk for unintentional fatal injuries. Using mortality data from 1993 to 2007 for the Agricultural Health Study (AHS), a cohort study of pesticide applicators and their spouses in North Carolina and Iowa, the researchers found that although all-cause mortality was significantly lower than expected, there was a four-fold increase in machine-related deaths. Mortality from motor vehicle non-traffic accidents and collisions was also elevated.

The study also found that certain types of cancers are more common among farmers. Using relative standardized mortality ratios to control for the fact that farmers tend to be healthier than the general population, researchers found that the relative mortality ratios were higher for cancers such as lymphohematopoietic, melanoma, prostate, and breast cancers. There were no elevations in chronic disease mortality from non-cancer outcomes. Team members suggest that an extended follow-up could provide new insights on the occupational hazards in agricultural populations.

*Citation:* Waggoner JK, Kullman GJ, Henneberger PK, Umbach DM, Blair A, Alavanja MC, Kamel F, Lynch CF, Knott C, London SJ, Hines CJ, Thomas KW, Sandler DP, Lubin JH, Beane Freeman LE, Hoppin JA. 2011. Mortality in the Agricultural Health Study, 1993-2007. *Am J Epidemiol* 173(1):71-83.

(Jeffrey Stumpf, Ph.D., is a postdoctoral fellow in the NIEHS Laboratory of Molecular Genetics Mitochondrial DNA Replication Group. Ritu Rana, Ph.D., is a visiting fellow in the NIEHS Laboratory of Toxicology and Pharmacology Human Metabolism Group.)

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# Inside the Institute

## Black History Month forum focuses on mental health

By Matt Goad

As part of Black History Month, the Research Triangle Park Chapter of Blacks In Government (BIG) and the NIEHS Diversity Council sponsored a program Feb. 23 on health issues in the African-American community. The theme for the forum, held in Rodbell Auditorium, was “Mental Health: The Good, the Bad, and the Ugly.”

Annette Rice, member of both BIG and the Diversity Council, said mental health is a major concern in the black community, because people often don't know where to turn for help.

### Wellness and the family

“Wellness is a focus for the entire family,” Rice said, “and, when you have one member with a risky behavior, the whole family is affected. There is help out there for the individual and for the family. We want to get the word out: Don't suffer in silence.”

To that end, Bill Smith, Nancy Kent, and Peter Baker of the [Durham Center](#) Local Management Entity spoke about options available to sufferers of mental illness and their families. Durham County, N.C., is the home to NIEHS.

Baker noted that when calling 911 for help with a mental health issue, people should always ask for a CIT, or Crisis Intervention Team, officer to ensure a police officer with training in mental health crisis issues is dispatched.

To personalize mental health issues, Ann Akland spoke about being a parent of a child with mental health issues. Akland, who is retired from the U.S. Environmental Protection Agency, dedicates her time to helping people with severe mental illnesses. Her passion for the cause comes from having a daughter with mental illness.

### Risky behavior

Also a topic for the forum was risky behavior, with William Zule, Dr.P.H., of RTI International, speaking about HIV, and Wendee Wechsberg, Ph.D., also of RTI International, speaking about substance abuse.

Risky behavior plays a large part in mental health issues, Rice noted, with the children of people who abuse drugs and pursue risky sexual behavior often suffering from mental health issues.



Workshop organizer, Rice, is the president of BIG, which collaborated with the NIEHS Diversity Council to co-sponsor the Black History Month forum on mental health. (Photo courtesy of Steve McCaw)



Chris Long, acting associate director for management, gave a hearty welcome to guest speakers and the audience. (Photo courtesy of Steve McCaw)

The forum was part of a continuing effort by BIG and the Diversity Council to bring attention to health issues of concern in the African-American community. Past forums have focused on lupus, breast cancer, prostate cancer, diabetes, and obesity.

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



*Zule spoke about HIV and risky behavior. (Photo courtesy of Steve McCaw)*



*Baker discussed Durham County services available to sufferers of mental illness and their families. (Photo courtesy of Steve McCaw)*

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## **NIEHS helps teachers learn how to teach science more effectively**

*By Matt Goad*

Teachers from across North Carolina gathered in Rodbell Auditorium Feb. 28 to draw on the resources of NIEHS to liven up their science lessons as part of the North Carolina Association for Biomedical Research (NCABR) “Prescription for Science Literacy” workshop.

Mary Grant, V.M.D., deputy chief of the NIEHS Comparative Medicine Branch, and Ericka Reid, Ph.D., NIEHS education outreach specialist, organized the workshop.

Workshop participants Sharon Beard, an industrial hygienist with the Worker Education and Training Program at NIEHS; Liam O’Fallon, a program analyst with the Susceptibility and Population Health Branch (SPHB) at NIEHS; and Regina Williams, program manager for [NCABR](#), gave opening remarks and an overview of the program for the day.



*Beard welcomed teachers from across North Carolina to the latest NCABR workshop in the 2010-2011 “Prescription for Science Literacy” series and told them about NIEHS Worker Education and Training programs. (Photo courtesy of Steve McCaw)*

The teachers toured NIEHS animal facilities, following a presentation by Grant on the humane use of animals in environmental health research at NIEHS. Grant noted that 99 percent of the animals used for testing at NIEHS are rats and mice, and that strict regulations mandate humane conditions for the animals.

### **Cancer, cell biology, and the environment**

Giving a presentation to the teachers on breast cancer and the environment was Les Reinlib, Ph.D., a health scientist administrator in SPHB. Reinlib explained that while genetics was long thought to be the driving force behind breast cancer, in recent years, two major studies have shifted that view to recognition of the important role played by environmental factors.

Michael Humble, Ph.D., a program administrator in the NIEHS Cellular, Organs, and Systems Pathobiology Branch, led the 29 teachers through several lesson plans involving cell biology and cancer, including exercises designed to teach about cancer and probability. In another exercise, the group was divided in half and charged with coming up with arguments for or against an imagined proposed law requiring people to cover 90 percent of their bodies when they are in the sun.

### **Practical knowledge**

“I got a lot that I could use,” said Margaret Raynor, a health occupation teacher at Clinton High School, singling out an exercise that used the flip of a coin and drawing of numbers to illustrate how several factors play into whether a person will get cancer.

Sue Ford, a biology and anatomy teacher at Rocky Mount High School, said the tour of the animal facilities gave her a new understanding of how many types of jobs were available to science students, an understanding that she plans to pass on to her students.

“Students don’t learn about the opportunities that are available to them,” Ford said.

The teachers received credit toward their continuing education and certification after completing the workshop.

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



*O’Fallon told the teachers about what NIEHS can offer them and their students, including curriculum development, teacher training, and summer intern opportunities. (Photo courtesy of Steve McCaw)*

## **N.C. Association for Biomedical Research**

NCABR is an organization dedicated to advancing all North Carolinians’ appreciation for the benefits of bioscience research and careers.

It is a statewide nonprofit organization founded in 1989 by North Carolina’s leading bioscience research institutions. Members include academia, industry, government, nonprofit research organizations and professional societies.

To date, more than 3,500 North Carolina K–12 teachers from 94 of the state’s 100 counties have participated in NCABR’s science education programs, more than 1,000 North Carolinians have attended an NCABR public forum to debate biomedical research issues, and dozens of members of the North Carolina and national media have attended an NCABR science journalism program.

The group’s “[Rx for Science Literacy](#)” workshop series is free for teachers in grades K-12.



*Diane Forsythe, D.V.M., center, chief of the Comparative Medicine Branch of NIEHS, led teachers on a tour of the animal facilities. (Photo courtesy of Steve McCaw)*



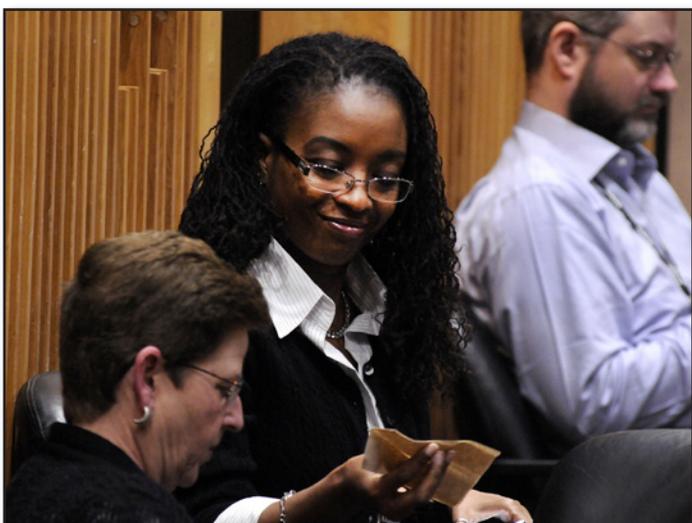
*Williams, left, and Alista "Cozzie" Watkins listened carefully to the presentations. Watkins teaches biomedical technology and medical science in the Charlotte-Mecklenburg [Phillip O. Berry Academy of Technology](#). (Photo courtesy of Steve McCaw)*



*Humble, standing, led teachers through a mock lesson on cell biology and cancer. (Photo courtesy of Steve McCaw)*



*Grant talked to the teachers about humane treatment of lab animals at NIEHS and the role of animal testing in environmental health research. (Photo courtesy of Steve McCaw)*



*Reid, center, consulted with Connie McElroy-Bacon of NCABR. Reid said she felt a lot of energy at the workshop, even late in the day. (Photo courtesy of Steve McCaw)*

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