

May 2014

## NIEHS Spotlight



### [Birnbaum featured at EPA Earth Day event](#)

On Earth Day, April 22, Birnbaum was featured by the EPA Cutting Edge Speakers Series, crafting the legacy of Earth Day into a charge for the future.



### [Board of Scientific Counselors advises NTP on draft concepts and more](#)

The BSC provided input to NTP at its April 17-18 meeting on peer-reviewed technical reports and draft concepts for Report on Carcinogens listings.



### [NIEHS and the Energy Future Coalition hold workshop on ultrafine particles from vehicle emissions](#)

NIEHS and EFC joined regulators, public health advocates, and journalists to discuss sources and health effects of ultrafine particles and polycyclic aromatic hydrocarbons.



### [Presentations and virtual forum mark Autism Awareness Month at NIEHS](#) ▶ Video

NIEHS hosted lectures by four experts in research on autism and the environment the morning of April 22, followed by a virtual community forum webcast that afternoon.

## Science Notebook



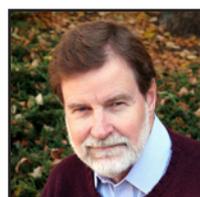
### [Falk lecture provides evolutionary insights into endocrine disruption](#)

Evolutionary biologist Joseph Thornton, Ph.D., fascinated the NIEHS audience, including family members of the late Hans Falk, Ph.D., with his research into why so many man-made substances mimic estrogen in the body.



### [Wetterhahn seminar highlights research on PCBs and type 2 diabetes](#)

In her April 3 Wetterhahn Award Series seminar, Nicki Baker, Ph.D., discussed her research into the mechanisms of the association between PCB compounds and diabetes.



### [Wilson honored with outstanding science award](#)

NIEHS senior researcher Samuel Wilson, M.D., received the prestigious 2014 SER-CAT Outstanding Science Award during a ceremony April 25 in Rockville, Md.



### [Scholars Connect Program marks second year](#)

NIEHS and NTP scientists gathered April 21 to recognize the accomplishments of a special group of young interns.

## NIEHS Spotlight



### [Centers focus on emerging environmental health science and collaboration](#)

Directors from across the U.S. gained expertise and new perspectives at the NIEHS Environmental Health Sciences Core Centers annual meeting, sponsored by USC.



### [Tsunami exercise helps prepare research community for disaster response](#)

NIEHS sponsored a table-top disaster response exercise April 7 in Los Angeles, to prepare researchers to take action in case of disaster.



### [The GuLF STUDY four years after the Deepwater Horizon oil spill](#)

On April 11, NIEHS provided preliminary findings and announced a second round of health exams, encouraging all participants to stay involved over the long term.



### [NIEHS grantee honored for autism research at White House ceremony](#)

Young-Shin Kim, Ph.D., received the PECASE award in a White House ceremony April 14, for her work researching environmental causes of autism.



### [SOT honors NTP and NIEHS researchers](#)

SOT specialty sections honored six researchers from NTP and NIEHS for outstanding achievements at the 2014 SOT conference.

## Science Notebook



### [Toxicology trainee honored for translational research](#)

For most graduate students, the Ph.D. is the highest point of the academic experience, but for NTP trainee Madisa Macon, Ph.D., the degree comes with an added distinction.



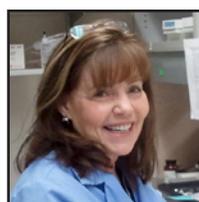
### [Unexpected protein partnership has implications for cancer treatment](#)

NIEHS scientists identified two proteins that together increase inflammation and may alter tumor growth, a finding that may help chemotherapy patients.



### [Arsenic in well water may diminish intelligence in children](#)

An NIEHS-funded study, published April 1, finds exposure to arsenic in drinking water is associated with lowered IQ among children in several Maine school districts.



### [NIEHS-funded researchers discover novel compound that could treat autoimmune diseases](#)

Oregon State University researchers, funded by NIEHS, screened thousands of compounds and found one that may treat autoimmune disorders with fewer side effects.



### [Core Day highlights resources available to NIEHS researchers](#)

Core facilities and support groups at NIEHS gathered in Rodbell Auditorium April 7 to showcase the support they can provide to Institute scientists.

## NIEHS Spotlight



### [NIEHS postdocs awarded NIH K99 grants](#)

Two NIEHS trainees have received coveted K99 grants from NIH, providing 1-2 years of mentored research and funds for supplies and participation in national meetings.



### [Sharing excitement about health and science at the NC Science Festival](#)

Volunteers from NIEHS share excitement about science, health, and science-related careers at local events during the North Carolina Science Festival.

## Inside the Institute



### [Discovery Lake gets a spring-cleaning](#)

NIEHS volunteers emerged from labs and offices to pick up trash and debris along the shoreline of Discovery Lake, helping maintain a healthy local environment.



### [Invasive-pest specialist enlightens NIEHS in Earth Week lecture](#)

Alonzo Suazo, Ph.D., educated an eager NIEHS audience on invasive species threatening North Carolina forests and actions underway to control them.

## Science Notebook



### [Exposure science in the 21st century](#)

Sponsored jointly by NIEHS and EPA, Rutgers professor Paul Liroy, Ph.D., spoke April 3 on exposure science and the need for collaboration across environmental health fields.



### [Chris Weis elected to ABT board of directors](#)

At the March SOT meeting, the American Board of Toxicology elected NIEHS toxicology advisor Chris Weis, Ph.D., to its board of directors.



### [Distinguished Lecture Series to welcome Christopher Wright, Ph.D.](#)

Developmental biologist Christopher Wright, Ph.D., of Vanderbilt University will present the next distinguished lecture May 6 at 11:00 a.m. in Rodbell auditorium.



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

The May issue of Environmental Health Perspectives focuses on the emerging One Health movement and growing concern — and controversy — over low-level exposures to arsenic.

## Calendar of Upcoming Events

- **May 2**, in Keystone 1003AB, 2:00-3:00 p.m. — Biomolecular Screening Branch Seminar Series with Lisa Truong, Ph.D., discussing “Multi-Dimensional Rapid Throughput Screening of ToxCast Phase I and II Chemicals Using Embryonic Zebrafish”
- **May 5-6 (offsite event)**, in the James B. Hunt Library at North Carolina State University, 8:00 a.m.-5:30 p.m. — “Collaborative Workshop on Aquatic Models and 21st Century Toxicology”
- **May 6**, in Rodbell Auditorium, 11:00 a.m.-noon — Distinguished Lecture Series presentation on “Reprogramming Within the Pancreas and Endoderm: Biological-Therapeutic Connections,” by Christopher Wright, Ph.D.
- **May 6**, in Rall D450, noon-1:00 p.m. — Receptor Mechanisms Discussion Group Seminar Series presentation on “Tissue-specific Functions of SIRT1 in HNF1alpha/FXR Signaling and Systemic Bile Acid Homeostasis,” by Xiaoling Li, Ph.D.
- **May 11-16 (offsite event)**, at the Renaissance Tuscany Il Ciocco Resort in Lucca, Italy — Gordon Research Conference, “Environmental Endocrine Disruptors: An Integrated Perspective From Wildlife to Human Health”
- **May 13-14**, in Rodbell Auditorium, 8:30 a.m.-5:00 p.m. — National Advisory Environmental Health Sciences Council meeting
- **May 14**, [NIH Webcast](#), 2:00-4:00 p.m. — Office of Research on Women’s Health National Women’s Health Week Scientific Forum
- **May 15**, in Rodbell Auditorium, 10:00 a.m.-noon — NIEHS Ethics Day with presentations by Kathy Hudson, Ph.D., Justina Fugh, J.D., and Meave Tooher, J.D.
- **May 22**, in Rodbell Auditorium, 8:30 a.m.-5:30 p.m. — NTP Technical Reports Peer Review Meeting
- **May 29**, in Keystone 1003AB, 10:00-11:00 a.m. — Keystone Scientific Seminar Series, featuring John Stegeman, Ph.D., speaking on “Plankton to P450: Models and Mechanisms at the Convergence of Oceans and Human Health”
- View More Events: [NIEHS Public Calendar](#)

## Extramural Research

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

- [Silicone wristbands as personal passive samplers](#)
- [Exposure to bisphenol A linked with early-onset prostate cancer](#)
- [Possible new autoimmune disease treatment without side effects](#)
- [Methylation in the adult mammalian brain](#)

## Intramural Research

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

- [Risk factor for lung disease in premature infants](#)
- [A fresh look at the genetics of breast cancer](#)
- [Humans with APOE4 gene more prone to inflammation](#)
- [Regulation of alternative polyadenylation is required for ESC self-renewal](#)

# NIEHS Spotlight

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## Birnbaum featured at EPA Earth Day event

*By Kelly Lenox*

NIEHS and NTP Director Linda Birnbaum commemorated Earth Day April 22 in her keynote address, “Our Environment, Our Health, Our Future,” at the U.S. Environmental Protection Agency (EPA) in Research Triangle Park (RTP), N.C.

Birnbaum, a former EPA scientist and senior manager, was greeted by a warm, enthusiastic crowd. John Vandenberg, Ph.D., national director for the EPA Human Health Risk Assessment Program, introduced Birnbaum with a hearty “Welcome home, Linda!” referring to her 19 years of service with EPA.

### **Environment influences human health**

Throughout her talk, Birnbaum emphasized the role environment plays in human health. In spite of progress in fighting infectious disease, environmental factors contribute to 85 percent of human disease worldwide, including the increasing incidence of noncommunicable conditions. Referring to the growing understanding of the role of gene-environment interaction, she noted, “You can’t change your genes, but you can change your environment.”

The term environment is commonly used to refer to food and diet, industrial and agricultural chemicals, and physical agents, such as ultraviolet radiation. However, Birnbaum reminded the audience that environmental factors also include influences such as the microbiome, or all the microorganisms that live in the body; lifestyle choices; psychosocial stress; and even prescription drugs.

### **The environment is indoors, too**

Birnbaum focused her talk on factors that current research is finding to cause health effects of previously unknown type or degree. These exposures may come from environmental degradation, such as air pollution and dioxin contamination, as well as household substances prevalent in industrialized society, including flame retardants, pesticides, and endocrine-disrupting chemicals like phthalates.

Research into the health effects of naturally occurring substances is enlarging our understanding of their impacts, as well. Birnbaum pointed to a new finding of decreased cognitive function associated with even low levels of arsenic in drinking water (see [story](#)). “These cognitive shifts are similar to what we’ve seen with lead,” she said.



*“Innovation and collaboration will be key to solving our 21st century environmental challenges and protecting human health,” said Birnbaum. (Photo courtesy Brian Hoffman)*

## Prevention is the key

As scientific understanding of the contribution of genetic and environmental factors, both individually and together, increases, we have new opportunities to make choices that improve health on a global scale, Birnbaum noted. For example, as we learn more about the impact of indoor air pollution from cookstoves, we can work to develop ones with lower emissions.

Replacement chemicals should also be carefully evaluated. After use of certain flame-retardant chemicals was banned, use of other substances increased. Now, environmental scientists are beginning to find evidence of their adverse health effects as well (see [story](#)). “We have to ask the right questions. Are the newer replacement chemicals any safer?” she said.

In closing, Birnbaum highlighted the NIEHS focus on global environmental health, climate change, and environmental impacts on vulnerable populations. “We have a tremendous opportunity to protect human health,” said Birnbaum. “Prevention is the key.”

The event was hosted by the Cutting Edge Speakers Series Committee and the EPA-RTP Management Council.

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## Board of Scientific Counselors advises NTP on draft concepts and more

*By Robin Mackar*

The NTP Board of Scientific Counselors (BSC) [met](#) April 17-18 in Rodbell Auditorium to provide input on several draft evaluation concepts and evaluate findings in draft reports recently peer-reviewed.

Topics included Report on Carcinogen (RoC) draft concepts for [cobalt](#), [goldenseal root powder](#), and selected [viruses](#); the peer-review outcome of four draft technical reports; and two draft concepts from the NTP Office of Health Assessment and Translation ([OHAT](#)).

### Report on Carcinogens

Ruth Lunn, Dr.P.H., director of the RoC office, summarized the [December](#) peer-review meeting on ortho-toluidine, used to make rubber, and the wood preservative pentachlorophenol and by-products of its synthesis. The new BSC chair, Lisa Peterson, Ph.D., of the University of Minnesota, attended the peer-review meeting as BSC liaison. “The science NTP presented was strong and discussions among the reviewers and NTP were quite animated and constructive,” Peterson said.

Gloria Jahnke, D.V.M., presented the draft RoC concept on Epstein-Barr virus, human immunodeficiency virus type 1, human T-cell lymphotropic virus type 1, Kaposi sarcoma-associated herpes virus, and Merkel cell polyoma virus. She noted that NTP will prepare a separate monograph for each virus, but RoC listing, should it occur, would include all the viruses together. The RoC already lists 3 viruses as known to be human carcinogens.



*Birnbaum provided updates about the budget, strategic plan, and scientific advances.  
(Photo courtesy of Steve McCaw)*

After the presentation by Diane Spencer of NTP on the draft RoC concept for the popular botanical supplement goldenseal root powder, BSC members discussed relevant doses, studies that should be included in the evaluation, and how to consider other ingredients in goldenseal preparations, before offering support for moving forward.

Spencer also addressed the draft RoC concept for cobalt, a naturally occurring metal. NTP and BSC discussed what mechanisms might drive the development of tumors noted in some studies and what forms of cobalt should be evaluated. Overall, the board expressed support for moving forward with this concept, but several reviewers commented that NTP should specify the forms of cobalt to be reviewed.

### Technical reports

NTP toxicologist Chad Blystone, Ph.D., updated the board on the [October](#) peer-review meeting for the draft technical reports on cobalt metal, vinylidene chloride, tetrabromobisphenol A, and glycidamide.

Richard Miller, D.V.M., Ph.D., of GlaxoSmithKline and BSC liaison to that meeting, gave positive feedback on both the meeting itself and the studies investigating molecular signatures of the tumors.

### Draft concept presentations

Kembra Howdeshell, Ph.D., of OHAT, presented the draft [concept](#) for evaluating literature on pregnancy outcomes associated with traffic-related air pollution. She described her team's preliminary literature search of nearly 18,000 unique scientific references, pared down to those addressing health effects, and finally to about 300 studies that included pregnancy outcomes. "When we found this good pocket of literature on pregnancy outcomes, we decided to focus our evaluation on the associations between pregnancy outcomes and traffic-related air pollution," Howdeshell said.

David Dorman, D.V.M., Ph.D., of North Carolina State University, and Sonya K. Sobrian, Ph.D., of Howard University College of Medicine, stressed the need to more clearly define what is meant by traffic-related air pollution. "You are taking on a daunting subject," Sobrian said. Both suggested that OHAT wait until the CDC completes its evaluations on pregnancy outcomes before proceeding too far with this concept.

NIEHS and NTP Director Linda Birnbaum, Ph.D., and NTP Associate Director John Bucher, Ph.D., both thanked the board for their helpful comments on this issue. "Your comments are making us realize how difficult it is to evaluate a project so early in the process. We will give more thought into how to get public input early," Birnbaum said.



*Blystone presented four draft NTP technical reports that were peer-reviewed in October. (Photo courtesy of Steve McCaw)*



*New BSC member Milton Brown, M.D., left, of Georgetown University Medical Center, and Gayle DeBord, Ph.D., who serves as the National Institute for Occupational Safety and Health liaison to NTP. Brown said many people use goldenseal for a variety of ailments, including as an alternative to some cancer treatments. (Photo courtesy of Steve McCaw)*

Another draft concept Howdeshell presented to the board was to systematically review the scientific evidence for adverse health effects associated with occupational exposure to cancer chemotherapy agents. The BSC strongly supported pursuing this evaluation.

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



*BSC members Robert Chapin, Ph.D., left, of Pfizer, and Sobrian discussed some of the concepts being presented during a break. (Photo courtesy of Steve McCaw)*



*Lisa Peterson, Ph.D., center, of the University of Minnesota, served ably as the BSC chair, with Bucher, left, and NTP Deputy Division Director for Science, Nigel Walker, Ph.D. (Photo courtesy of Steve McCaw)*



*Dorman had insightful comments and questions on many of the meeting topics. (Photo courtesy of Steve McCaw)*



*Howdeshell presented two draft OHAT concepts at the meeting, receiving an abundance of welcome comments from the BSC. (Photo courtesy of Steve McCaw)*



BSC member Iris Udasin, M.D., of Robert Wood Johnson Medical School, was especially supportive of the OHAT draft concept related to occupational exposure to cancer chemotherapy agents. (Photo courtesy of Steve McCaw)



Lunn, left, and Jahnke review their slides together before their presentations. (Photo courtesy of Steve McCaw)



RoC's Spencer gave a show-and-tell of goldenseal root powder, which can be easily purchased at local stores. (Photo courtesy of Steve McCaw)

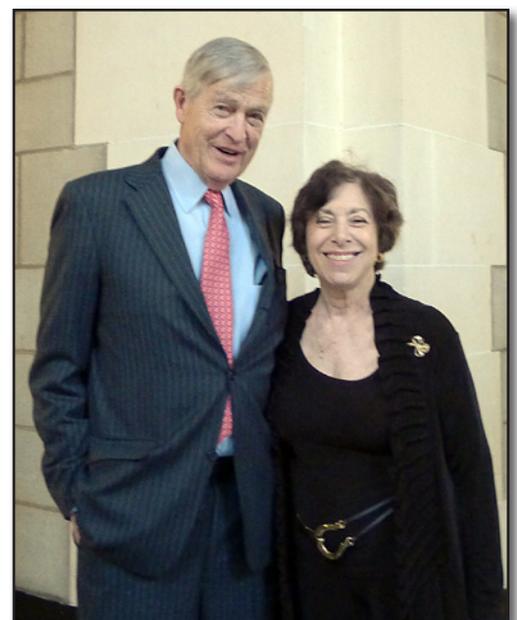
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## NIEHS and the Energy Future Coalition hold workshop on ultrafine particles from vehicle emissions

By Paula Whitacre

NIEHS and the Energy Future Coalition (EFC) joined forces April 1 at a [workshop](#) exploring the health impacts of ultrafine particles (UFPs) from vehicle emissions. Hosted by the Institute of Medicine and held at the National Academy of Sciences in Washington, D.C., scientists invited to speak at the event faced the challenge of presenting their findings to an audience of both scientists and nonscientists, including regulators, public health advocates, and journalists.

NIEHS and NTP Director Linda Birnbaum, Ph.D., described the purpose of the meeting in her opening remarks. “This workshop assembles a panel of leading researchers to present the current state of our knowledge on the potential effects of UFPs with aromatics, as well as the research strategies needed to address this emerging environmental public health issue,” she said.



The workshop grew out of conversations between Wirth, left, and Birnbaum. (Photo courtesy of Paula Whitacre)

Former Colorado Sen. Timothy Wirth, a co-founder of EFC, stressed the need for such an event. “The data seem to be coming in at a rapid and somewhat remarkable rate, and our timing for having this discussion seems to me to be about perfect,” he said.

### Sources and characteristics of fine and ultrafine particles

In the morning session, scientists discussed recent advances in knowledge about polycyclic aromatic hydrocarbons (PAHs), and coarse (10 microns), fine (2.5 microns), and ultrafine (nanosized) particles. Underscoring how much remains unknown, several speakers observed that UFPs might cause greater damage than their mass would suggest. “Mechanisms, composition, size, and host factors contribute to the complexity,” observed [Dan Costa, Sc.D.](#), of the U.S. Environmental Protection Agency.

According to [Staci Simonich, Ph.D.](#), of Oregon State University, China and India are the world’s largest PAH emitters, but the U.S. emits the most per person. Her lab has shown that air masses containing PAHs routinely travel great distances, such as across the Pacific Ocean.

[Andre Nel, M.D., Ph.D.](#), of the University of California, Los Angeles (UCLA), stressed that the toxicological effects of fine and ultrafine particles differ, as do pulmonary retention and impacts. “Ultrafine particles go deeper into the lung,” he said. “UFPs are likely to go to sites where the pathophysiology of disease is more important.”

### Human health effects

Birnbaum moderated the afternoon discussion on research, funded in part by NIEHS, into health effects of UFPs and PAHs. [Frederica Perera, Ph.D.](#), of Columbia University, presented her findings on associations between PAH exposure and neurodevelopmental disorders. [Beate Ritz, M.D., Ph.D.](#), of UCLA, summarized her lab’s research on air pollution’s link with autism and low birth weight.

[Jim Zhang, Ph.D.](#), of Duke University, analyzed data from his Beijing Olympics study, where there was a clear difference in air pollution before, during, and after the games — particularly in the levels of UFPs containing PAHs — as well as associated lung function and cardiovascular conditions. Finally, [Douglas Brugge, Ph.D.](#), of Tufts University, discussed community participatory research on UFP exposure and health.

Several common threads wove through the talks. For instance, certain populations have greater exposure, due to living near roadways or other sources of UFPs. Panelists also stressed that the diseases they studied involve multiple factors. But, as Ritz noted about autism, if environmental factors account for even 10 percent of the 8,000 cases she studied, that means 800 fewer cases.



*NIEHS grantees and staff participating in the workshop included, from left, Perera, Zhang, Birnbaum, Nel, Ritz, and Sri Nadadur, Ph.D., program director for the NIEHS NanoHealth and Safety program. (Photo courtesy of Paula Whitacre)*



*Workshop breaks provided further discussion time for grantees Simonich, left, and Perera. (Photo courtesy of Paula Whitacre)*

## Policy implications

A closing discussion, facilitated by Wirth and EFC co-founder C. Boyden Gray, J.D., involved the audience in exploring policy implications. Topics included the key role of roadway traffic, a call for technological improvements in vehicles and fuels, and the need to distinguish effects of UFPs from those of other particulates.

One participant stressed the importance of shifting the emphasis. “Most people think of air pollution as a minor irritant,” said Robert Musil, Ph.D., president and CEO of the Rachel Carson Council. “We need to focus the problem around public health.”

(Paula Whitacre is a contract writer with the NIEHS office in Bethesda, Md.)

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## Presentations and virtual forum mark Autism Awareness Month at NIEHS

By Eddy Ball

NIEHS hosted lectures by four experts on [autism and the environment](#) the morning of April 22, followed by a virtual community forum webcast in the afternoon, which had 270 pre-registrations.

The speakers in the Minisymposium on Autism and the Environment (see [text box](#)) joined NIEHS and NTP Director Linda Birnbaum, Ph.D., for a question-and-answer session. Cindy Lawler, Ph.D., lead representative for [NIEHS-funded autism activities](#), moderated the symposium and webcast, which coincided with [National Autism Awareness Month](#).

The presentations at the minisymposium and the afternoon panel discussion outlined the results of research that underscores the important role of environmental factors in autism and related disorders. According to the forum participants, autism is a complex condition triggered by the intricate interplay of multiple genetic and environmental factors. The events associated with autism may take place before conception or during the especially sensitive time of prenatal development, adding to the difficulty of teasing out specific causes.

Birnbaum set the tone of the forum with her opening remarks. “The rate of autism spectrum disorder [ASD] continues to rise in this country [now approaching 2 percent], and we’re really working hard to understand why,” she said. “We believe that many factors are behind this increase in rates. It can’t just be genetics. Something in our environment may also be playing a role.”



*In response to a request from Lawler, right, Volk described the classic autism phenotype of impaired language and social adaptation. (Photo courtesy of Steve McCaw)*



**Linked video:**  
[Watch as panelist Heather Volk, Ph.D., describes her findings about gene-environment interactions and autism risk \(01:32\)](#)

(Launches in new window)

Download Media Player:  Flash [↗](#)

## Translating research into public health awareness

The virtual forum on autism and the environment was the second virtual forum in a series of [community forums](#) hosted by NIEHS. The first, in 2012, explored [obesity and the environment](#).

“This virtual forum complements an ongoing series of community forums that we’ve been having for years,” Lawler at the beginning of the webcast event. “At some of our recent ones, we’ve talked about safe seafood in Seattle, traffic pollution in Los Angeles, asthma in Boston, and the Gulf oil spill in New Orleans. With this virtual forum [on autism], we’re extending the conversation to a national and even international audience on a topic of global significance.”



*Reichenberg, left, and Hertz-Picciotto have looked at parental age as factors in the development of autism in offspring. (Photo courtesy of Steve McCaw)*

## Exploring the interplay of genetics and environment

Participating in the virtual forum panel with Birnbaum were four leading researchers, who are receive NIEHS funding for their work and are pioneers in efforts to discover environmental contributions to the increasing incidence of autism. Their responses to questions from viewers reflected the intriguing, but still preliminary findings from recent research about what may contribute to ASD and, just as importantly, what may be protective against it.

- [Alan Brown, M.D.](#), commented on the role of the immune system and suggested that pregnant mothers exercise special caution about exposure to infection. He also pointed to folic acid supplementation as a possible preventive strategy. Brown has studied a marker of inflammation in mothers, C-reactive protein (CRP), that is significantly associated with autism, especially for mothers with protein levels in the highest 20 percent.
- [Irva Hertz-Picciotto, Ph.D.](#), underscored Birnbaum’s remarks by observing, “It’s not either [genetics]/or [environment]... In most cases, you can’t pin it on one factor.” Her research has pointed to birth timing and nutritional deficits as possibly playing a role in autism, and she suggested vitamin supplements before and during pregnancy, as well as a 3-year interval between pregnancies.
- [Avi Reichenberg, Ph.D.](#), reported on the association of preterm birth and low birth weight with autism. He said large-scale twin studies show a role for heredity, but he also noted that even with identical twins fewer than half of the pairs share an autism diagnosis.
- [Heather Volk, Ph.D.](#), discussed her findings that a specific genetic variation increases risk for autism, but only when it is combined with high exposure to traffic pollution.

The speakers called for more research to inform more effective preventive measures. According to Birnbaum, the NIEHS funding commitment to autism research has exceeded \$40 million over less than ten years and continues to be a priority.

The virtual forum on autism was organized by the NIEHS Division of Extramural Research and Training, Office of Science Education and Diversity, and Office of Communications and Public Liaison.

## Minisymposium on Autism and the Environment

Also hosted by Lawler, the minisymposium featured four 20-minute presentations followed by a question-and-answer session:

- Hertz-Picciotto of the University of California, Davis MIND Institute, discussed “Environmental Chemicals, the Intrauterine Environment, and Child Neurodevelopment.” She offered insights into early views of a condition caused by mothers who failed to adequately nurture their children, a now-discredited theory most prominent in the work of Bruno Bettelheim, M.D. She reflected on her 13 years researching autism, beginning at a time when little attention was paid to the environment. She said, “Our focus [now] is on modifiable factors.”
- Reichenberg, of the Ichan School of Medicine at Mount Sinai and Seaver Center for Autism Research and Treatment, in a talk on “Familial Risk for Autism” described his meta-analysis of studies of twins. He found that genetic factors can’t fully explain risk for ASD, and that environmental factors may be responsible for a large percentage of risk. His work has also uncovered a high rate of other conditions that coexist with ASD and an association with parental age.
- In his talk on “The Prenatal Envirome and Autism: New Insights from a National Birth Cohort Study,” Brown, a professor at Columbia University, described new potential biomarkers for autism risk, such as elevated C-Reactive Protein, IL-6, and IGF-1, as well as evidence of higher levels of persistent organic pollutants in mothers of ASD children. He has also found an association between the trajectory of childhood head growth and autism.
- Looking forward to her new grant from NIEHS, Volk, of the Keck School of Medicine at the University of Southern California and the Saban Research Institute at Children’s Hospital Los Angeles, discussed her work in “Moving From Environmental Effects to Gene and Environment Interaction in ASD.” In her study of exposure to air pollution in Los Angeles, Volk geocoded addresses at the time of birth to estimate levels of exposure to traffic pollutants based on local traffic-related sources and regional air quality measures. She found that increased prenatal exposure was associated with language and social adaptation deficits when combined with a common variant in the receptor tyrosine kinase gene, pointing to underlying gene and environment interaction.



*The panel, as viewers worldwide saw on the webcast, included, from left, Birnbaum, Reichenberg, Hertz-Picciotto, Brown, Volk, and Lawler. (Photo courtesy of Steve McCaw)*

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# Centers focus on emerging environmental health science and collaboration

By Joe Balintfy

Directors and staff from across the country found fresh perspectives on emerging environmental health sciences at the 2014 NIEHS Environmental Health Sciences [Core Centers](#) annual meeting, hosted by the University of Southern California (USC) April 7-9 in Los Angeles.

Presentations on environmental contributions to obesity and the effects of environmental agents on the brain anchored the agenda. With a Disaster Research Response Tabletop Exercise (see [story](#)) beforehand, and a community forum on public health, smart growth, and land use planning afterwards (see sidebar), the meeting provided center directors with diverse experiences and new expertise, to enrich the programs they oversee.

“There were cutting edge science and new opportunities for collaboration and multidisciplinary research, not just in the talks, but also through the interaction of the groups,” said meeting host, Frank Gilliland, M.D., Ph.D., director of the Southern California Environmental Health Sciences Center and professor of preventive medicine at the USC Keck School of Medicine.

## Scientific partnerships foster cutting-edge research

NIEHS Environmental Health Sciences Core Centers tackle problems such as identifying toxic substances in the environment and learning how they affect people’s health. Centers approach these key issues with a variety of methods.

## Community forum unites public health, smart growth, and land use planning

Deciding where to put a park or create access to walking and cycling in a big city is not easy. The best intentions, such as building housing near mass transit stops and creating urban gardens, may have unintended consequences, including increased exposure to traffic pollution and food grown in soil that may be contaminated. To help find solutions, scientists, urban planners, and community groups met for a community forum, hosted by NIEHS, the [Southern California Environmental Health Sciences Center](#), and the USC-Children’s Environmental Health Center.

“As we learn more about how the environment influences our health, it is very important to connect communities like this,” said Birnbaum. “In the research community, we want to hear what’s happening related to local planning and public health.”

The forum included short presentations and a poster session where representatives from 17 local community [groups](#) described their work — and the challenges they face — to center scientists, NIEHS staff, and other participants.

“The poster session was a high point,” said Gilliland. “I think the community forum was innovative in that it allowed the researchers and policymakers to interact free form with community group leaders, with lots of great opportunities for learning and exchanging ideas.”

“It was wonderful to have such a cross-sector discussion on the impact of land use and urban planning on public health,” said Scott Chan, program director for the Asian and Pacific Islander Obesity Prevention Alliance, one of the community groups displaying a poster.

This community forum was the latest in a [series](#). “Each community forum is different because ideas percolate from local stakeholders,” said John Schelp, NIEHS special assistant for community engagement and outreach. “In this one we took a 45-minute break to look at displays from community groups, and everyone came back to the following session. So folks were truly engaged.”

“We’re a very diverse group of centers,” said Joe Beckman, Ph.D., the center director at Oregon State University. He said it was important for the directors to meet together to build understanding of the range of scientific challenges across the country. “And it’s important to find out what’s happening at NIEHS.” That perspective was shared by NIEHS staff as well as NIEHS and NTP Director Linda Birnbaum, Ph.D.

“These core centers are adept at building partnerships,” said Birnbaum, pointing out that the centers can continue working together through supplement funding, which encourages cross-center collaborations, working groups, and using online meeting tools. “In this electronic age, there are more ways that we can get together — and work well together — such as webinars.”

### “Grease our neurons”

The meeting included scientific presentations, administrative meetings, and Community Outreach and Engagement Core (COEC) sessions.

“These activities grease our neurons so we can start thinking about how we can adapt our science and engineering to address the problems the community perceives,” explained John Essigmann, Ph.D., professor of biological engineering and chemistry at the Massachusetts Institute of Technology (MIT), and director of the MIT Center for Environmental Health Sciences. He called the scientific sessions excellent. “They were very accessible, to the point where I could relate what was being presented to other branches in environmental health sciences,” Essigmann said.

### Collaboration through communication

COECs build and sustain multi-directional bridges between the centers and their communities, both scientific and public, to identify and address environmental health concerns. Attendees shared various tools being used to measure environmental exposures, including UV dosimeters and passive wristbands, to answer questions community residents have about exposures, as well as to educate students about environmental exposures and health. Sessions included discussions on using social media to boost COEC and center goals, by developing communication strategies that include blogs, science cafes, and videos.



*Kafi Blumenfield, who serves on the Recreation and Parks Commission for the City of Los Angeles, gave one of the community forum presentations. (Photo courtesy of Amanda Shaffer)*



*Alina Bokde of the Los Angeles Neighborhood Land Trust described her group’s work to create small parks and gardens, to help remedy the critical lack of green space in the city’s underserved neighborhoods. (Photo courtesy of Amanda Shaffer)*



*Jose Hernandez of the East LA Community Corporation explained his group’s work to build affordable housing and engage in community planning. (Photo courtesy of Amanda Shaffer)*

“I think these center meetings have evolved to really provide a lot of opportunities for the kind of communication that is so critical for advancing science,” Gilliland concluded.

(Joe Balintfy is a public affairs specialist in the NIEHS Office of Communications and Public Liaison.)

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## Tsunami exercise helps prepare research community for disaster response

By Joe Balintfy

What would happen if a magnitude 9.1 earthquake struck Alaska, generating a tsunami that hit the ports of Los Angeles and Long Beach, Calif., stirring up toxic substances from Superfund sites, oil refineries, and sewage treatment plants along miles of coastline? Scientists, community leaders, and state and local health organizations met in Los Angeles April 7 to discuss this not-so-far-fetched scenario, and to practice incorporating health researchers into immediate response and recovery efforts.

The exercise was a first step in the new [NIH Disaster Research Response Project](#), a pilot project developed by NIEHS and the National Library of Medicine to create a disaster research system consisting of coordinated environmental health disaster research data collection tools and a network of trained research responders.

“We have a long history at NIEHS of engaging in research related to disasters, from the 9/11 World Trade Center attack, to Hurricanes Katrina, Ike, and Sandy, and the Gulf oil spill,” said NIEHS and NTP Director Linda Birnbaum, Ph.D. “The sooner we can get into the disaster site and start collecting data, the more we can learn about the health effects that may result,” she added.

NIEHS Senior Medical Advisor [Aubrey Miller, M.D.](#), emphasized that, in every disaster, saving lives is the first priority, but acknowledged there is a real need for scientific data, as well. “There are research questions that we need to be thinking and talking about that run parallel to what’s going on in the lifesaving side of the house.”



*The ports of Los Angeles and Long Beach receive 40 percent of all imports to the U.S., mostly from Asia, and are close neighbors to surrounding communities. (Photo courtesy of Joe Balintfy)*



*Hughes, right, introduces Stephanie Ross, Ph.D., a geophysicist with USGS and coordinator for the [Science Application for Risk Reduction Tsunami Scenario](#), the basis for the Disaster Research Response Tabletop Exercise. (Photo courtesy of Joe Balintfy)*

## Both an up-close perspective and bird's eye view

The tabletop exercise started with a bus tour that stopped first at a community sandwiched between a major freeway and an oil refinery, giving participants a sobering view of potential human exposures during a disaster. The tour continued to a park overlooking the ports of Los Angeles and Long Beach, which together form the largest container port complex in the U.S., and the fifth largest in the world.

One of the tour hosts, Andrea Hricko, of the Southern California Environmental Health Sciences Center at the University of Southern California, explained that harbor communities experience the combined impacts of production and storage of fossil fuels, together with traffic around the ports. According to Hricko, the ports are the single largest source of air pollution in Los Angeles.

“It’s a huge port complex and international gateway, which means there are a lot of ships in the harbor, cranes, diesel-fueled trucks, thousands of containers, and fuel storage facilities,” she said. “And, if there were a tsunami, you can picture the refineries catching fire and oil spills from fuel storage tanks and barges.”

## A disaster that hasn't happened in 50 years

The exercise included certain assumptions — for example, half a million people are affected by blocked roads, power outages, and fires. Participants discussed when and how it would be appropriate and safe to start research. First responders, worker organizations, state and local health departments, and federal agencies collaborated to expand recovery plans to include trained research responders.

Joseph (Chip) Hughes, director of the NIEHS Worker Education and Training Program, pointed out that the tsunami scenario used in the exercise was based on one developed by the U.S. Geological Survey (USGS). “One of the great things about this activity is that our agencies have been able to partner and develop our tabletop exercise from their scenario,” said Hughes, with a reminder that an earthquake in Alaska caused a tsunami 50 years ago.

(Joe Balintfy is a public affairs specialist in the NIEHS Office of Communications and Public Liaison.)

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*Linda Delp, Ph.D., director of the University of California, Los Angeles, Labor Occupational Safety and Health Program, explained that the Los Angeles basin is home to nearly 13 million people, 60 percent of California's workforce, 20 active and former Superfund sites, and eight major refineries. (Photo courtesy of Ted Outwater)*



*Hughes, front left, is one of more than 135 people, including researchers, health experts, and government leaders, who participated in the Disaster Research Response Tabletop Exercise. (Photo courtesy of Joe Balintfy)*

# The GuLF STUDY four years after the Deepwater Horizon oil spill

By Robin Mackar

On April 20, 2010, the Deepwater Horizon rig exploded in the Gulf of Mexico, releasing more than 210 million gallons of oil. NIEHS, as part of the federal government's response, provided safety training for the more than 100,000 volunteer cleanup workers and initiated the [GuLF STUDY](#) (Gulf Long-term Follow-up Study) — the largest study ever conducted on the potential health effects of an oil spill.

In an April 11 teleconference, Dale Sandler, Ph.D., lead researcher for the GuLF STUDY and chief of the NIEHS [Epidemiology Branch](#), updated members of the media, the public, and study participants on the progress of the study. More than 30 reporters participated in the call, and in the days that followed, several hundred media outlets published stories about the GuLF STUDY. On April 17, Sandler presented a similar overview to NIEHS staff, at the request of [David Miller, Ph.D.](#), head of the NIEHS Laboratory of Toxicology and Pharmacology.

## Stay engaged, get second health exam

Sandler emphasized that while much progress has been made, study participants need to stay involved over the long term. Researchers are contacting all participants to conduct telephone interviews on current health status. In addition, they are inviting participants living within 60 miles of Mobile, Ala. and New Orleans to take part in a second comprehensive health exam.

NIEHS has partnered with health clinics at the [University of South Alabama College of Medicine](#) and [Louisiana State University Health Sciences Center School of Medicine](#) to conduct the health exams, which will focus on neurological, respiratory, and mental health issues.

Although designed for study purposes only, researchers will provide participants with the results of blood pressure, cholesterol, and diabetes screenings. They will also make referrals for health care, as needed. During the original health exams, researchers referred more than 500 participants to primary care providers for health concerns.

## Preliminary observations

Preliminary observations from the first round of health exams indicated that cleanup workers were about 30 percent more likely to have moderate to severe depression than residents who did no cleanup work. Results were similar for anxiety.

“It’s important that the 33,000 people enrolled in this study stay involved, because these early findings need to be followed up over time,” said Sandler. “At this point, it is hard to know if the increased frequency of depression and anxiety in workers is because of exposure to oil and dispersants, or something else about the oil spill experience and its aftermath.”

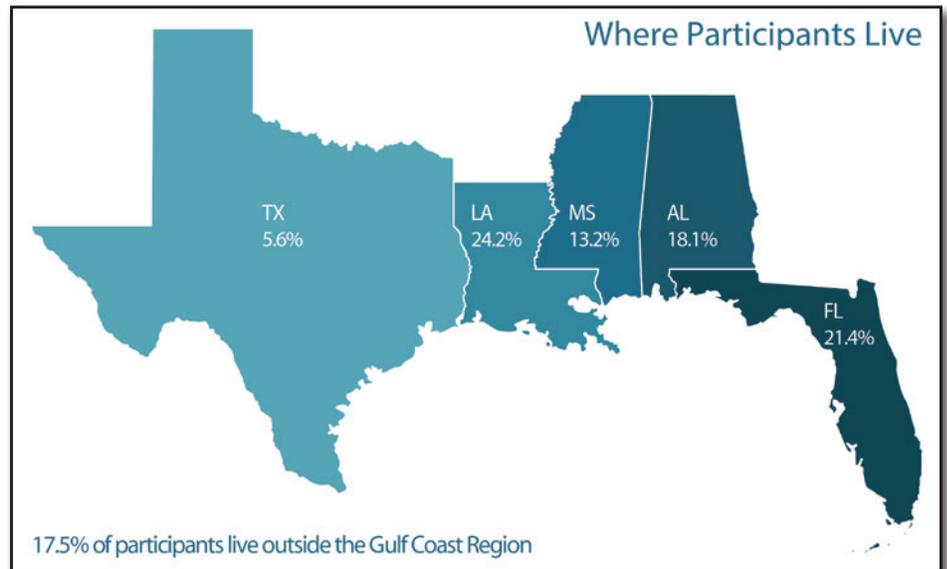


*Sandler is lead researcher on the GuLF STUDY, which seeks to better understand whether exposure to the oil and dispersants may lead to short-term or long-term health effects in workers and volunteers who helped with the cleanup efforts. (Photo courtesy of Steve McCaw)*

Sandler explained that the research team initially focused on the mental health effects of the spill, because high levels of anxiety, depression, and stress are frequently reported after disasters. “People in Gulf communities have been through so much,” she said. “Many have lost their jobs, and there is a lot of general, everyday stress and uncertainty in their lives.”

“The bottom line is that we really need the GuLF STUDY participants to stay engaged. If they haven’t already done so, we encourage them to call 1-855-NIH-GULF (1-855-644-4853) to schedule their follow-up interview and to participate in the health exam and other study activities,” Sandler said.

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



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## NIEHS grantee honored for autism research at White House ceremony

By Nancy Lamontagne

NIEHS grantee Young-Shin Kim, M.D., Ph.D., received a prestigious Presidential Early Career Award for Scientists and Engineers April 14 for her groundbreaking autism research and commitment to community service. NIEHS nominated her for the award, which is the highest honor the United States government gives to early-stage scientists and engineers. By studying the role of environmental risks and gene-environment interactions, [Kim](#) seeks to understand why the prevalence of autism spectrum disorder (ASD) is increasing.

Kim joined 102 scientists and engineers receiving the awards at a ceremony in Washington, D.C. John Holdren, Ph.D., director of the White House [Office of Science and Technology Policy](#), gave the keynote address. President Obama then greeted the group at the White House and thanked them for their outstanding achievements.

“It is a great honor to be chosen for this acknowledgment that my research is changing the field and also contributing to the community,” said Kim, an associate professor in the Child Study Center at the Yale University School of Medicine. “I want my work to benefit the community right now, not just in the future.



*The Presidential Early Career Awards recognize pursuit of research at the frontiers of science and technology, and commitment to community service, as demonstrated through scientific leadership, public education, or community outreach. Kim credits the support she received from all her mentors for helping her to advance her career. (Photo courtesy of Young-Shin Kim)*

I try hard to educate the community about autism, help teachers understand the importance of identifying children with autism, and find ways to provide services to children experiencing any type of difficulties.”

### **Are more children developing autism?**

The latest [study](#) from the Centers for Disease Control and Prevention (CDC) estimates that 1 in 68 children have ASD. The prevalence has more than doubled in a decade, and scientists aren’t sure why. Kim explains that looking at prevalence, or the number of children with autism at a given time, isn’t the best approach to determine if more children are really developing autism. “Prevalence can change because of increased public awareness, better screening, study design, and other reasons,” Kim said. “The way to understand if more children are developing autism is to use a prospective study to look at incidence.” A prospective incidence study looks at new cases in a healthy population over time.

In 2012, Kim received NIEHS funding to conduct a 5-year prospective, incidence study in South Korea. Each year, her research team directly screens all 7-year-olds — about 7,000 children — who were born in Goyang city, South Korea. Children confirmed to have ASD, as well as their families, are invited to join the study and donate blood samples. Screening all the children born in the city, even if they have moved, ensures a truly representative sample of children with ASD. For comparison, the researchers are also enrolling children without autism, matched in terms of sex and IQ.

### **Environmental influences**

The researchers will use the blood samples to identify genes and exposures that are involved in ASD. They will look at a wide variety of preconception and prenatal factors, including exposures that parents encounter at work, the age of the father, alcohol and tobacco use, medications, and exposures to environmental contaminants, such as pesticides. “Because the influence of genetic factors is unlikely to change from year to year, if we find an increase in cases of autism, then it is strong evidence that environmental factors are at work,” Kim said.

Cindy Lawler, Ph.D., lead of the NIEHS Autism Research Program, recommended Kim for the award. “Education and advocacy are an integral part of Kim’s daily work,” Lawler said. “She has shown that delivering reliable, evidence-based knowledge and skills to the broad community can lead to reductions in stigma, changes in policy, and improvement in the lives of youth and families facing bullying, ASD, and other conditions.”

“In short,” Lawler concluded, “Kim remains an active clinician and educator, as well as community activist and advocate.”

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

## **Understanding autism prevalence**

In 2011, Kim published a [study](#) in which her research team directly screened all children aged 7-12 — about 55,000 — in a South Korean community. She found that 1 in 38 children had autism, much higher than the CDC estimates.

Kim explained that most studies use clinics and special education programs to identify children with autism, because scientists assume that autism is severe enough for children to need services. She found that those studies were missing children with autism who were high-functioning and didn’t use services.

Kim plans to use her award for a pilot study that will follow children from the 2011 study into adulthood. She wants to better understand the differences between high-functioning children with autism and those who used services, and whether environmental factors can predict outcomes in these two groups.

# SOT honors NTP and NIEHS researchers

By Shannon Whirledge

The 53rd annual meeting of the Society of Toxicology (SOT) provided an opportunity for NIEHS and NTP scientists to showcase their research to a global audience (see [story](#)). As in years past, at this year's conference March 23-27 in Phoenix, SOT specialty sections honored the outstanding work of trainees and researchers, through awards for outstanding achievement within each specialty.

## Excellent training

Several awardees credited their achievements to their exceptional training at NIEHS and NTP. "NIEHS and NTP have been a huge part of my training," said Rachel Goldsmith, Ph.D.

Katie Pelch, Ph.D., agreed. "Training here at NIEHS has been great, because I've been able to interact with, and collaborate with, so many different people studying many diverse topics," she said. "The research for which I won the award is definitely different than what I had previously studied, but it has been a good opportunity for me."

## Expert mentorship

In addition to institutional support, mentors also received warm thanks. Salik Hussain, D.V.M., Ph.D., said his mentor, Stavros Garantziotis, M.D., has been tremendously supportive, allowing him to ask novel research questions. "Stavros has always encouraged me to develop autonomy and scientific rigor," he said. "He also provided me with multiple opportunities to lead projects and train post-baccalaureate students, to polish my skills as an independent investigator."

Goldsmith also acknowledged the guidance of her mentor. "Jonathan Freedman, Ph.D., provided the ideal combination of support and independence, making it possible for me to be successful in my postdoc," she said.

## Opportunities for collaboration

Collaborative opportunities further enhance the experience of trainees and researchers at NIEHS and NTP. "Here at the NIEHS, my mentor, Barry McIntyre [Ph.D.], has encouraged me to build upon my background in nanotoxicology by working with Nigel Walker [Ph.D.] on NTP projects involving nanomaterials," said Brian Sayers. "Recognizing the need to broaden my expertise, both have ensured that I have the opportunity to work on

## SOT Awards to NIEHS and NTP

### Postdoctoral awards

- Rachel Goldsmith, Ph.D., Emil A. Pfitzer Postdoctoral Award, Drug Discovery Toxicology Specialty Section
- Salik Hussain, D.V.M., Ph.D., Outstanding Postdoctoral Fellow, Nanotoxicology Specialty Section
- Olive Ngalame, Ph.D., Postdoctoral Award for Research Excellence, Stem Cell Specialty Section
- Katie Pelch, Ph.D., Third Place Postdoctoral Award, Metals Specialty Section

### Publication and abstract awards

- Kembra Howdeshell, Ph.D., Best Abstract, Mixtures Specialty Section
- Brian Sayers, Ph.D., Best Publication Award, Nanotoxicology Specialty Section

### Recognition of service

- Barry McIntyre, Ph.D., Past President to Reproductive and Developmental Toxicology Specialty Section
- Erik Tolker, Outgoing Service as Secretary/Treasurer of Stem Cell Specialty Section

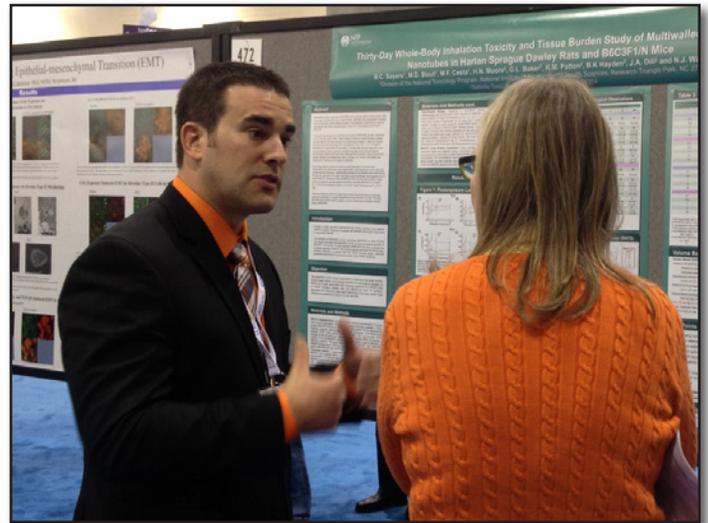
other projects.”

Kembra Howdeshell, Ph.D., health scientist with NTP, was selected out of a pool of 60 as the recipient of an abstract award. Her publication represented data obtained through collaboration between EPA and NIEHS to evaluate the developmental effects of *in utero* exposure of different phthalate mixtures on the male reproductive tract. Cynthia Rider, Ph.D., also of NTP, is also an author on the paper and worked on mathematical modelling of chemical mixtures for the study.

(Shannon Whirlledge, Ph.D., is an Intramural Research Training Award (IRTA) fellow in the NIEHS Laboratory of



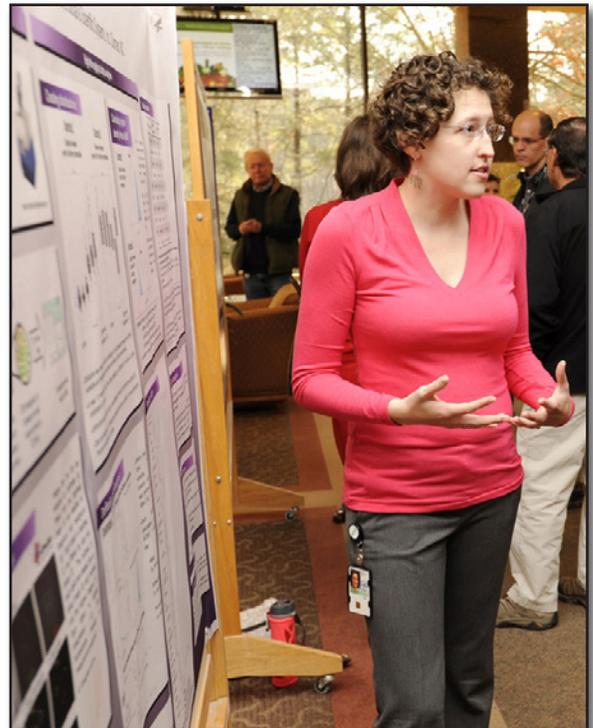
Hussain is a visiting fellow with the NIEHS Office of Clinical Research. (Photo courtesy of Steve McCaw)



Sayers is an IRTA fellow in the NTP Toxicology Branch. (Photo courtesy of Nigel Walker)



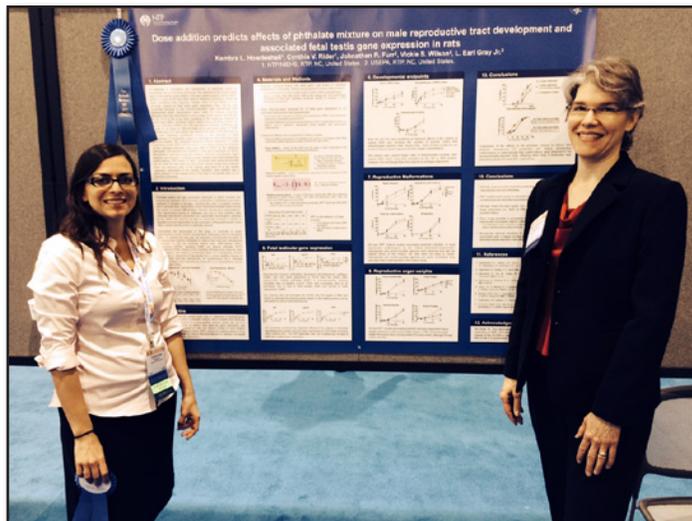
Ngalame is a postdoctoral fellow with the NTP Inorganic Toxicology Group. (Photo courtesy of Steve McCaw)



Goldsmith is an IRTA fellow in the NTP Biomolecular Screening Branch. (Photo courtesy of Steve McCaw)



*Pelch is an IRTA fellow in the NTP Office of Health Assessment and Translation (OHAT) and in the Inorganic Toxicology Group. (Photo courtesy of Steve McCaw)*



*Howdeshell, right, is a health scientist in the OHAT. Rider is a toxicologist in the NTP Toxicology Branch. (Photo courtesy of Robin Mackar)*

Signal Transduction.)

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## NIEHS postdocs awarded NIH K99 grants

*By Robin Arnette*

The goal of the National Institutes of Health [Pathway to Independence \(PI\) Award](#), also known as the K99/R00 program, is to increase the number of independent, NIH-supported researchers in the United States. For postdoctoral fellows interested in running their own labs one day, the program offers just the blend of mentoring and training they'll need to be successful.

NIEHS has two K99 winners this year in Natalie Gassman, Ph.D., a member of the DNA Repair and Nucleic Acid Enzymology Group, headed by Samuel Wilson, M.D., and Shannon Whirlledge, Ph.D., a member of the Molecular Endocrinology Group, led by John Cidlowski, Ph.D.

During the K99 phase, which corresponds to 1-2 years of mentored research, Gassman and Whirlledge will receive competitive salaries and funds that cover research supplies and attendance at national meetings. After completing the K99 portion, if they land tenure-track positions at academic institutions, they may apply for an independent R00 that lasts up to 3 years, and increases their salary and research support.

### DNA repair and BPA

Since Gassman works in a DNA repair group, she wanted to combine DNA repair analysis with one of the Institute's traditional research priorities, bisphenol A (BPA). She said a literature search yielded many instances of BPA exposure linked to DNA damage, but not many investigators specifically examined repair mechanisms.

"I thought it was a nice opportunity to take the DNA repair expertise of the lab and have it look at this environmental toxicant that's of great interest," Gassman said. "I plan to have my own research angle that I can,

hopefully, take with me to a new position at a research university.”

Wilson said that Gassman’s project falls right in the middle of a long-standing interest of his group — studying how cells experiencing oxidative stress adjust their repair mechanisms in response to BPA. So far, Gassman’s K99 work is off to a good start. Her preliminary results have uncovered a striking BPA cellular phenotype.

### **Glucocorticoid receptors and genistein**

When Whirlledge joined Cidlowksi’s group in 2009, she began working on a project that examined the interplay between glucocorticoid receptors and stress signaling in the uterus. To understand the interaction, she and her colleagues developed a tissue-specific knockout mouse line, in which the rodent uterus lacked glucocorticoid receptors.

She wondered whether receptors for glucocorticoid and those for the well-known sex hormone estrogen played a role in reproductive functions. For her K99 research, she intends to take that project one step further.

“I want to look at the interaction between estrogens and glucocorticoids in the uterus using genistein,” Whirlledge said. “If estrogen and glucocorticoid receptors diminish each other’s effect in the uterus, I’ll be able to determine that by using a molecule that has environmental importance.” Genistein is structurally similar to estrogen and occurs naturally in soy.

As Whirlledge’s mentor, Cidlowksi said he’s certain she will be able to make the transition from postdoc to lead researcher because she is independent and has the drive to go after hard scientific questions.

### **Helping the transition**

Since its inception in 2006, the K99/R00 program has provided a bridge for many young scientists transitioning from trainee to experienced researcher. Gassman and Whirlledge can now add their names to this list and feel confident their new careers as principal investigators will get a boost from this funding.

“The support researchers receive during the early years of their careers really gives them a leg up on their competition,” said NIEHS Scientific Director Darryl Zeldin, M.D. “I encourage all NIEHS postdocs to write K99 proposals.”

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*Before coming to NIEHS to study DNA repair, Gassman focused on cancer research at the Comprehensive Cancer Center of Wake Forest University, Winston-Salem, N.C. (Photo courtesy of Steve McCaw)*



*Whirlledge won best oral presentation March 8 at the North Carolina Triangle Consortium for Reproductive Biology. [Story] (Photo courtesy of Steve McCaw)*

# Sharing excitement about health and science at the NC Science Festival

By Simone Otto

NIEHS volunteers helped spread awareness and excitement about science and health April 5 at the Triangle SciTech Expo. The expo was held at the North Carolina Museum of Natural Sciences and was one of two events NIEHS participated in during the [2014 North Carolina Science Festival](#).

The volunteers promoted science literacy, sparked children's imaginations, and taught the public about science-related careers. By all accounts, this year's events were a huge success.

Located on the main floor of the museum, the NIEHS table saw a lot of traffic. Younger children were especially fascinated with extracting strawberry DNA. Huei-Chen Lao, NIEHS coordinator of K-12 Science Education and Outreach, expertly supervised many of these extractions, engaging youth of every age with questions, and helping them to understand science methodology and its relevance to their lives.

On the other end of the table, participants tested lung capacity, while volunteers graphed the results. Husbands and wives, parents and children, and groups of friends enjoyed trying to outdo each other in lung capacity. Combined with the smoker's lung demonstration, it sparked frequent discussions about smoking and lung health.

The demonstration of a smoker's lung versus a healthy lung, using BioQuest® Inflatable Lungs, attracted the most attention from young and old alike. The youngest made faces and backed away from the smoker's lungs. Others were excited to put on a pair of gloves and feel the lungs inflate and deflate.

"Wow, that is cool!" was the reaction of Jadea, age 5, from Cary, N.C.

Many festival participants came over specifically to see the lungs, either because they were studying the subject in school, or because they knew a smoker and were hoping to convince them to quit. Several former smokers reaffirmed their decision to quit smoking, and a few smokers were shocked enough that they expressed interest in quitting. Quite a few festivalgoers even thanked the scientists for providing this demonstration.

"This is our third year, and the first time doing three activities at once! It was so great, and the lungs were an absolute hit with every age group," said Ericka Reid, Ph.D., NIEHS Office of Science Education and Diversity (OSD) director.

## Volunteers

Miranda Bernhardt, Ph.D.  
Joanne Damborsky, Ph.D.  
Bernd Gloss, Ph.D.  
Cathy Jamison  
Huei-Chen Lao  
Caitlin McDonough, Ph.D.  
Simone Otto, Ph.D.  
Robert Petrovich, Ph.D.  
Ericka Reid, PhD.  
Alisa Suen, Ph.D.  
Misty Thomas, Ph.D.  
Erica Ungewitter, Ph.D.



*NIEHS volunteer Otto, left, inflates lungs in a demonstration of healthy versus smoker's lungs. The young festivalgoer asked about the differences between the lungs while her parents looked on. (Photo courtesy of Simone Otto)*

In addition to participating in the Triangle SciTech Expo, NIEHS staff also volunteered at the March 30 Family Science Fair at the Marbles Kids Museum. OSED provided supplies, and NIEHS fellows supplied volunteers for this successful outreach.

“It was very rewarding to see the audience totally engaged in the hands-on activities that we provided,” said Lao. “Most importantly, we helped them to realize that science is relevant to daily life.”

(Simone Otto, Ph.D., is an Intramural Research Training Award (IRTA) fellow in the NIEHS Ion Channel Physiology Group.)



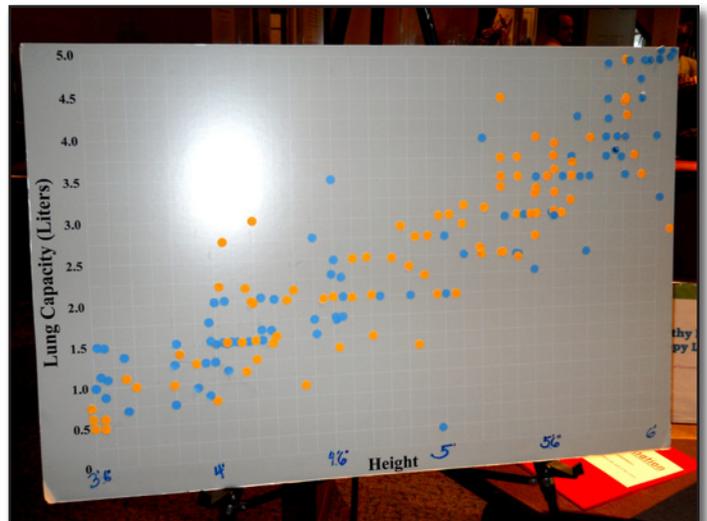
*Extracting strawberry DNA impresses a young participant and his family. (Photo courtesy of Simone Otto)*



*Many future scientists enjoyed the science of strawberry DNA extraction at the Triangle SciTech Expo. (Photo courtesy of Simone Otto)*



*NIEHS fellow Ungewitter, left, helped festival participants test their lung capacity — an activity that became surprisingly competitive. (Photo courtesy of Simone Otto)*



*Each lung capacity test result was plotted and color-coded for the person's sex. Several hours of testing indicate lung capacity exhibits a linear relationship with height, regardless of the sex of the participant. (Photo courtesy of Simone Otto)*



*NIEHS volunteer Damborsky, center, managed the lung capacity activity, while Reid, right, inflated the lungs, demonstrating effects of smoking on lung capacity. (Photo courtesy of Simone Otto)*



*Lao, left, taught an intrigued young girl and her father about DNA, in the strawberry DNA extraction activity. (Photo courtesy of Simone Otto)*



*Earlier in the week at the Marbles Kids Museum Family Science Fair, Thomas, right, helped two young scientists extract strawberry DNA. (Photo courtesy of Hardin Engelhardt)*

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# Science Notebook

## Falk lecture provides evolutionary insights into endocrine disruption

By Robin Arnette

Evolutionary biologist Joseph Thornton, Ph.D., was invited to NIEHS April 14 to present the 2014 Hans L. Falk Memorial Lecture. His talk, “The Evolutionary History of Steroid Hormone Receptors: Ancient Insights Into Endocrine Disruption,” focused on what he’s learned about the evolution of steroid hormone receptors and the implications for endocrine disruption. The seminar was hosted by David Armstrong, Ph.D., head of the NIEHS Membrane Signaling Group.

Thornton said he chose to study steroid hormone receptors because they are often the targets of environmental toxicants, and they are excellent models for studying the evolution of protein complexity.

What’s the connection between evolution and endocrine disruption? “If we want to understand why a biological process exists, or what makes it normal or abnormal, we need to understand its history,” Thornton said, “as, in society, understanding the current state of our culture or politics is greatly enriched if we understand how it got this way.”

### Bringing the past back to life

As members of a larger nuclear receptor superfamily, steroid hormone receptors play crucial roles in the regulation of metabolism and have key functions in the development of cancer and endocrine disruption. Each receptor binds a particular hormone, such as estrogen or cortisol, with extraordinary affinity and specificity.

To study the evolutionary processes that led to this specificity, Thornton’s team developed a strategy called ancestral gene resurrection, which involved cloning the genes from many primitive organisms, testing which hormones could activate them efficiently, and determining their three-dimensional structures at the atomic level.



*Thornton is a professor in the Department of Human Genetics, and Department of Ecology and Evolution at the University of Chicago. He is also a professor at the Center of Ecology and Evolutionary Biology at the University of Oregon. (Photo courtesy of Steve McCaw)*



*Armstrong, head of the NIEHS Membrane Signaling Group, hosted the seminar. (Photo courtesy of Steve McCaw)*

Using this information, the researchers examined a large database containing gene sequences of present-day steroid receptors and developed a phylogenetic tree, a diagram that shows evolutionary relationships among species. Next, Thornton's team employed a statistical method, which relied on models of the evolutionary process, to examine the probability of an amino acid mutating to another amino acid across the tree. Once they generated plausible genetic sequences, they synthesized DNA to code for those ancestral proteins, expressed them in cultured cells, and characterized their functions biochemically.

## Genetic divergence

The results suggested that the first steroid receptor was an estrogen receptor that evolved approximately 450 million years ago. This estrogen-specific steroid receptor 1 (SR1) gave rise to an SR2, which bound to progesterone rather than estrogen. Thornton's data suggested that the new function occurred as a result of metabolic changes that produced new hormones, as well as genetic variation in the receptor that made it selective for a new hormone.

"Once we were able to identify the mutations that caused the evolutionary changes in function," Thornton explained, "we used structural biology to understand the physical mechanisms that mediated ancient genetic change and the effect on estrogen receptors."

Thornton summed up the implications for endocrine disruption by pointing out that receptors evolved to be only as specific as necessary. Before the evolution of additional hormones and the gene duplications that gave rise to the extended steroid receptor family, there was little pressure on the original receptor to be very precise. This helps explain why so many environmental toxicants, or xenoestrogens, can activate estrogen receptors and thereby disrupt normal physiological processes.

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*NIEHS Calcium Regulation Group head James Putney, Ph.D., foreground, and Scientific Director Darryl Zeldin, M.D., to his left, were part of the full house attending the lecture. (Photo courtesy of Steve McCaw)*



*NIEHS Deputy Director Richard Woychik, Ph.D., presented Thornton with the Hans L. Falk Memorial plaque, as members of the Falk family looked on. Shown, from left, are Woychik, Thornton, Raymond Falk, Ph.D., Gabrielle Falk, and Donald Falk, M.D. Falk's widow has attended every one of the Falk lectures. (Photo courtesy of Steve McCaw)*

# Wetterhahn seminar highlights research on PCBs and type 2 diabetes

By Sara Mishamandani

The Superfund Research Program (SRP) Karen Wetterhahn Memorial Award seminar at NIEHS April 3 featured [Nicki Baker, Ph.D.](#), professor of health sciences at Baker College. A former NIEHS-funded University of Kentucky SRP grantee, Baker received the 2012 Wetterhahn Memorial Award for her doctoral work on how coplanar polychlorinated biphenyls (PCBs) can affect the development and severity of type 2 diabetes.

## Exposure to PCBs and Diet

Epidemiological studies have noted a link between PCB exposure and type 2 diabetes. Baker discussed how she explored potential mechanisms for that link by measuring glucose and insulin intolerance in mice exposed to PCB-77, a form of PCB present in the environment. In mice fed a low-fat diet, PCB-77 exposure resulted in glucose and insulin intolerance. When mice were fed a high-fat diet, however, scientists observed no PCB-77 effect on glucose and insulin intolerance.

Because of the discrepancy between mice fed different diets, Baker explored how PCB exposure affected mice experiencing weight loss. She found that when obese mice lost weight, those exposed previously to PCB-77 lost the ability to maintain stable blood glucose levels, known as glucose homeostasis, that is generally seen with weight loss. Thus, for the exposed mice, weight loss was not as effective in preventing type 2 diabetes.

## Understanding the mechanism

Baker and her team also wanted to see how PCBs interact with the aryl hydrocarbon receptor (AhR), a protein involved in the regulation of a number of biological responses. In particular, they were interested in its connection to glucose and insulin resistance in adipocytes, or fat cells. Using mice deficient in adipocyte AhR, Baker's team observed that the mice did not develop the glucose and insulin intolerance usually induced by PCB-77, suggesting that adipocyte AhRs may be responsible for the ability of PCB-77 to impair glucose homeostasis during weight loss.



During her day at NIEHS, Baker, left, met with Suk and other staff, to discuss her work at the University of Kentucky as an NIEHS-funded trainee. (Photo courtesy of Steve McCaw)



SRP program administrator Danielle Carlin, Ph.D., right, introduced Baker and acknowledged her contributions to research and the community. "Nicki knows what she wants to achieve and, as a result, works diligently and responsibly in all aspects of her project," Carlin said, quoting Baker's mentor, Lisa Cassis, Ph.D. "On her own initiative, she is serving as a role model for future scientists studying environmental chemicals." (Photo courtesy of Steve McCaw)

They next tested the antioxidant resveratrol, a compound found in wine, peanuts, chocolate, and other foods, to determine if it helps protect against diabetes induced by PCB-77. In mice fed low-fat diets and levels of resveratrol similar to those found in dietary supplements, scientists observed that PCB-77 did not impair glucose and insulin tolerance.

According to Baker, these studies suggest the adipocyte AhR plays a potentially significant role in the development of diabetes and obesity, and that resveratrol may represent a novel therapeutic approach for PCB-exposed populations.



*Suk, left, listens as NIEHS and NTP Director Linda Birnbaum, Ph.D., one of the many audience members who participated in discussions after the talk, addressed continuing efforts by NIEHS to investigate the association between PCBs and diabetes. (Photo courtesy of Steve McCaw)*

### **Celebrating Karen Wetterhahn**

SRP Director Bill Suk, Ph.D., began the seminar with a tribute to [Karen Wetterhahn, Ph.D.](#), an expert in the mechanisms of metal toxicity and founding member of the Dartmouth SRP center. She died tragically in 1997 from dimethylmercury poisoning, caused by the accidental spill of a few drops of the chemical on her latex glove-covered hand.

“The recipients of the Wetterhahn Award are not only doing outstanding science, they also work with the community at large, and they are mentors to other students,” said Suk. “That is the purpose behind this award, because this was a large and important component of Karen Wetterhahn’s life.”

In addition to research, Wetterhahn was passionate about teaching. Concerned about the higher dropout rate of women studying science compared to men, she worked with a colleague to develop the Women in Science Project at Dartmouth.

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

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## **Wilson honored with outstanding science award**

*By Eddy Ball*

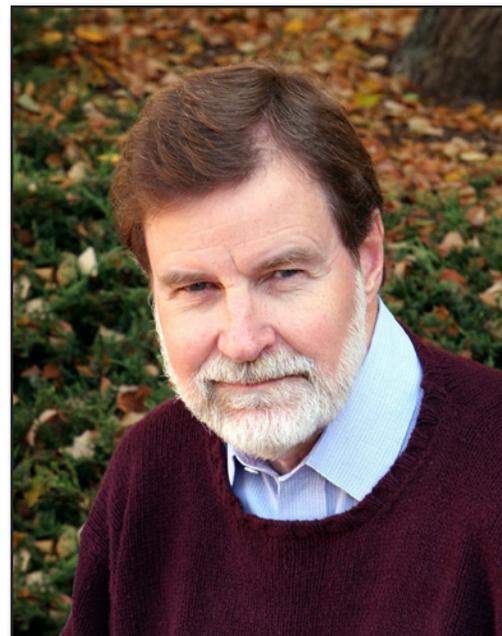
NIEHS senior researcher Samuel Wilson, M.D., received the prestigious 2014 SER-CAT Outstanding Science Award during a ceremony April 25 in Rockville, Md., joining just ten other top scientists who have been so honored since the organization established the award in 2005. [Wilson](#), who heads the DNA Repair and Nucleic Acid Enzymology Group, received an award plaque and delivered an invited lecture on the research related to his award.

The Southeast Regional Collaborative Access Team (SER-CAT) is an organization consisting of [21 member institutions](#), formed in 1997, to provide third generation X-ray capabilities to macromolecular crystallographers

and structural biologists in the southeastern region of the U.S. Located at the U.S. Department of Energy [Advanced Photon Source](#) at the Argonne National Laboratory in Illinois, SER-CAT held its [11th Annual Symposium](#) in conjunction with the 44th Mid-Atlantic Macromolecular Crystallography Meeting April 23-26 at the University of Maryland, at Shady Grove.

Wilson joins a [group of distinguished researchers](#) from three other NIH institutes and four major universities with leading biomedical research centers. He is the first NIEHS recipient of the SER-CAT Outstanding Science Award, although the organization honored visiting fellow Matthew Schellenberg, Ph.D., of the NIEHS Genome Stability Structural Biology Group headed by Scott Williams, Ph.D., with its Young Investigator Award in 2013.

In the organization's award letter to Wilson, SER-CAT Assistant Director and Science Award Committee Chair John Rose, Ph.D., of the University of Georgia, wrote, "Your paper, 'Observing a DNA Polymerase Choose Right from Wrong,' by Freudenthal et al., was judged by our review panel to have the highest scientific impact of all of the papers considered" (see [story](#)). The award committee also expressed its gratitude for Wilson's time and effort in demonstrating the technical capabilities of the SER-CAT facility in his research.



*Wilson has authored and co-authored more than 400 research and environmental health policy publications, and has been on the editorial board of several journals. From 1996 to 2009, he served as deputy director and acting director of NIEHS. (Photo courtesy of Steve McCaw)*

### **At the forefront of a rapidly advancing field**

As one of the powerful structural biology techniques, X-ray crystallography offers a unique perspective into the world of proteins, enzymes, and nucleic acids.

While much can be learned from amino acid or nucleic acid sequences, the strength of crystallography is in its ability to provide the important third dimension with 3-D snapshots of macromolecules involved in cell signaling, cellular disruption and defense, nucleic acid biology, and cell division. Due to its powerful nature, biochemists have been using crystallography to address questions ranging in size from small chemicals to large intermolecular protein interactions.

Wilson and his colleagues in the NIEHS Laboratory of Structural Biology enjoy an international reputation as leaders in their field, and Wilson's award adds to the prominence of NIEHS in this leading-edge research.

As NIEHS researcher Lars Pedersen, Ph.D., who has collaborated on a number of papers with Wilson's group, explained, "For many years, Sam's group has been on the forefront of using structural biology to understand the molecular details of how DNA polymerases function. The latest work by Bret Freudenthal is a great example of the contributions the Wilson lab has made in advancing the field. This award, along with Matt's award last year, demonstrates the quality of science that NIEHS is performing at SER-CAT. In addition, this work underscores how important it is to NIEHS to be a part of this outstanding consortium."

*Citation:* [Freudenthal BD, Beard WA, Shock DD, Wilson SH](#). 2013. Observing a DNA polymerase choose right from wrong. *Cell* 154(1):157-168. [Story Summary](#)



*The Advanced Photon Source provides the brightest storage ring-generation X-ray beams in the western hemisphere. SER-CAT emphasizes research employing advanced crystallography in the areas of de novo multi-wavelength and single-wavelength anomalous dispersion or MAD/SAD method of protein structure determination, high-resolution structural analyses, large unit cells, drug design, structural genomics, soft X-ray data collection, and next-generation beamline automation. (Photo courtesy of NIH)*

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## Scholars Connect Program marks second year

*By Eddy Ball*

NIEHS and NTP scientists gathered April 21 to recognize the accomplishments of a special group of young interns. Attendees heard talks by six young women who made up the second cohort of [participants](#) in the NIEHS [Scholars Connect Program \(NSCP\)](#), as they reported on yearlong projects mentored by lead researchers in NIEHS and NTP labs (see [text box](#)).

The program opened with an introduction by Erika Reid, Ph.D., director of the NIEHS [Office of Science Education and Diversity \(OSED\)](#), which oversees the NSCP. “It [NSCP] is a concerted effort to connect with colleges and universities in the Triangle,” she said, “to take further steps toward increasing and supporting the number of students from under-represented groups in the sciences and, specifically, the environmental health sciences.”

The talks, by students from St. Augustine’s College (SAC), North Carolina Central University (NCCU), North Carolina State University (NCSU), and the University of North Carolina at Chapel Hill (UNC), reflected the range of research underway at NIEHS and NTP, as well as the achievements of the interns and the quality of their intensive training and career development over the past academic year.

**Linked video:**  
[Watch this year's Scholars Connect interns at work and learn more about the program \(03:23\)](#)  
(Launches in new window)

Download Media Player:  Flash [↗](#)



Presentations were moderated by session chair [Janine Santos, Ph.D.](#), a staff scientist in the NIEHS Mammalian Genome Group, who was introduced by NSCP Program Coordinator Cathy Jamison.

### Starting almost from scratch

This year's projects were ambitious and almost uniformly took the young scientists far beyond their comfort zones and areas of previous academic preparation. Their academic training ranged from chemistry and public health to nutrition and environmental health, with only one participant bringing advanced training as a biology major to her internship at NIEHS.

The interns' research ranged from novel basic-science approaches to better understand major public health concerns, to a bioinformatics survey of an animal model used in NTP gold-standard two-year rodent assays. Each of the projects was part of a longer-range effort to address such issues as fibroids, asthma, targeted chemotherapy, diseases of the gastrointestinal tract, neuropathology, and evaluation of the toxicology and carcinogenicity of environmental chemicals.

Thanks to their extensive training and practice during their time at NIEHS, the presenters were poised and well prepared for questions about their study designs, methodology, and findings. Each articulated the big-picture public health significance of her research, as well as its limitations and its place in her group's long-range plans. Along with their many successes, the interns spoke candidly of false starts and failures as important parts of their learning experience.

The interns also demonstrated their grasp of the value of team science involving collaborations across the Institute and with external colleagues. Several of the projects took advantage of NIEHS core resources, such as ones offered by the Protein Expression Core and the Microarray Core.

### Moving forward

Whether this year's NSCP participants ultimately choose to pursue a career in the environmental sciences or not, they all expressed a deep appreciation of the training experience and the close relationships they developed with the mentors they worked alongside over the past year.

As she presented certificates to the scholars and their mentors, Reid expressed her own appreciation for the experience. "It has been an absolute pleasure," she said.

Meanwhile, Reid, Jamison, and K-12 Science Education and Outreach Coordinator Huei-Chen Lao are looking forward to the next academic year, as the program recruits participants for the upcoming Scholars Connect Boot Camp (see [story](#)) that will begin the program's third year.

*Understandably, the scholars may have been nervous, but, like Burks, they were comfortable thinking on their feet and even engaging in banter with the audience. (Photo courtesy of Steve McCaw)*



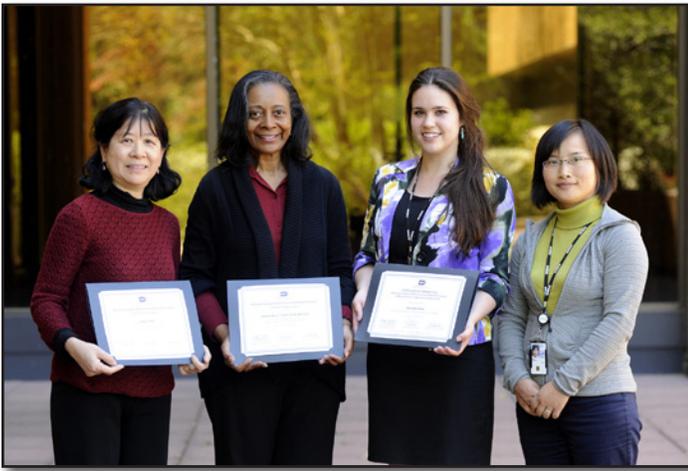
*Santos introduced the speakers and monitored questions from the audience. "I'm very proud for you, guys," she told the interns. (Photo courtesy of Steve McCaw)*



*Bushel was one of the many mentors on hand to support their interns. He also helped Burks answer a question about future directions from one of the scientists in the audience. (Photo courtesy of Steve McCaw)*



*Reid congratulated members of the second NSCP class, as she looked forward to greeting a new group in June. (Photo courtesy of Steve McCaw)*



*Several of the scholars took advantage a lovely spring day for photos on the patio. Shown, left to right, are Yu, Dixon, Blatchford, and research fellow Xiaohua Gao, M.D., Ph.D. (Photo courtesy of Steve McCaw)*



*Burks and Dunigan took a moment to show off their certificates. (Photo courtesy of Steve McCaw)*



*Oyelowo joined colleagues, from left, Harry Orihuela, and biologist Christopher McPherson, Ph.D. (Photo courtesy of Steve McCaw)*



*In addition to her lab family, Oyelowo's proud parents also joined her following the presentations. (Photo courtesy of Steve McCaw)*

## Scholar presentations

- **Kate Blatchford (NCSU)** — “The Contribution of Membrane Associated GPR-30/GPER in Nongenomic Signaling by Bisphenol A (BPA).” Mentored by NTP [Molecular Pathogenesis Group](#) leader Darlene Dixon, D.V.M., Ph.D., and biologist Linda Yu, M.D., Blatchford investigated the role of low-level exposure to an endocrine-disrupting compound in inducing cell proliferation and growth of uterine fibroids.
- **Mia Burks (SAU)** — “Genomic Regions in Mice Reveal a Molecular Landscape to Investigate.” Working with [Biostatistics Branch](#) head Clarice Weinberg, Ph.D., and staff scientist Pierre Bushel, Ph.D., Burks explored the effects of gene interaction and polymorphism in promoting susceptibility to spontaneous hepatocellular carcinoma in a rodent model used in NTP two-year assays.
- **Brittany Dunigan (SAU)** — “Knock Down of DNA Polymerase  $\beta$  in Xrcc1<sup>+/+</sup> and Xrcc1<sup>-/-</sup> Mouse Fibroblast Cells.” Mentored by [DNA Repair and Nucleic Acid Enzymology Group](#) leader Samuel Wilson, M.D., and staff scientist Julie Horton, Ph.D., Dunigan studied proteins involved in base excision repair of DNA damage in cancer cells for potential intervention by targeted chemotherapy.
- **Ashley Kang (NCSU)** — “Role of Sirt1 in Intestinal Epithelial Biology.” Kang worked with [Metabolism, Genes, and Environment Group](#) leader Xiaoling Li, Ph.D., and postdoctoral fellow Mallikarjuna Metukuri, Ph.D., on a study of the influence of the regulatory protein Sirt1 on nutrient absorption and health in the intestine, with possible implications for understanding inflammatory bowel disease, colon cancer, and Type-2 diabetes.
- **Melissa Kerr (NCCU)** — “Inter- $\alpha$ -Inhibitor Heavy Chains: Domain-based Functional Effects on Immune Cell Activation and Migration.” Working with [Matrix Biology Group](#) leader Stavros Garantziotis, M.D., and biologist Vandy Stober, Kerr explored the role of a protein heavy chain in airway inflammation and remodeling that contributes to respiratory diseases, including asthma.
- **Toyosi Oyelowo (UNC)** — “Inhibition of Microglial Polarization by Inorganic Arsenic.” Mentored by NTP [Neurotoxicology Group](#) leader Jean Harry, Ph.D., and postdoctoral fellow Ruben Orihuela, Ph.D., Oyelowo studied mechanisms of arsenic immune suppression and inhibition of the removal of bacteria from the central nervous system, which are linked to progressive neurodegeneration.

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## Toxicology trainee honored for translational research

*By Eddy Ball*

For most graduate students, the Ph.D. is the highest point of the academic experience, but for NTP trainee [Madisa Macon, Ph.D.](#), the degree comes with an added distinction. Even before she officially received her diploma, Macon took home a prestigious award for research that generates knowledge and innovative solutions to address critical societal needs — in her case, the public health impact of human exposure to endocrine-disrupting chemicals.

Along with the degree in toxicology she'll receive May 10 during graduation ceremonies at the University of North Carolina at Chapel Hill (UNC), Macon is one of 20 graduate students presented a 2014 Impact Award

from the UNC Graduate Education Advancement Board during the 16th Annual Graduate Student Recognition Celebration April 24 in Chapel Hill, N.C.

Macon is a trainee in the Reproductive Endocrinology Group of the NTP Laboratory, headed by her Intramural Research Training Award mentor and dissertation advisor, [Suzanne Fenton, Ph.D.](#) Macon studies the mechanistic basis of health effects following prenatal exposure to perfluorooctanoic acid (PFOA) in mice (see text box).

As the award committee wrote in its announcement of the winners, “Published data from Macon’s studies have already been used by two agencies in their human health assessment of PFOA toxicity. Her research has the potential to further inform regulatory agencies in North Carolina and beyond in their risk assessment of PFOA.”

### **Moving insights at the bench into public health**

In keeping with the NIEHS and NTP public health mission, Fenton’s group is deeply concerned with the potential public health impact of its studies of human disease, using mice and rat models, translating internal dose in animal models to known exposure levels in U.S. residents.

“Madisa has worked very hard for the sake of public health. She has performed her studies to help us understand the potential effects of children’s exposure to this harmful chemical,” Fenton explained. “Importantly, she has discovered modes of action for effects of PFOA in the breast, which seems to be a particularly sensitive target tissue. She is very deserving of this award.”

### **Advancing a career with support from NIEHS and NTP**

After completing her undergraduate work at Xavier University of Louisiana and a Master of Public Health degree at Drexel University, Macon joined Fenton’s group, at NIEHS,

## **PFOA and human health**

Fenton’s group is interested in the developmental effects of high-use or high-exposure environmental compounds, such as PFOA, also known as C8.

PFOA was a natural choice for research by the group. It is a long-chained perfluorinated chemical that does not occur naturally in the environment, and has special properties and hundreds of manufacturing and industrial applications, most notably in coatings for nonstick cookware. It meets the requirements as a chemical of interest for environmental scientists, because of its persistence in the environment and in the blood of the general U.S. population, as well as its demonstrated developmental and other adverse effects in laboratory animals.

Although regulatory action on PFOA currently resides at the state level, the [U.S. Environmental Protection Agency \(EPA\)](#) is working with major companies to reduce emissions and product content of PFOAs, with the goal of eliminating production and use of the chemical by 2015. In 2009, EPA issued Provisional Health Advisories that included PFOA, to protect against potential risk from exposure to the chemical through drinking water.

EPA nominated PFOA for [NTP study](#) in 2003. Since then, NTP scientists and contractors have performed short-term toxicity, long-term carcinogenicity, and a range of special studies on the compound. In a Sept. 20, 2013 announcement in the [Federal Register](#), NTP listed PFOA among twenty new substances nominated for possible review for future editions of the [Report on Carcinogens](#).

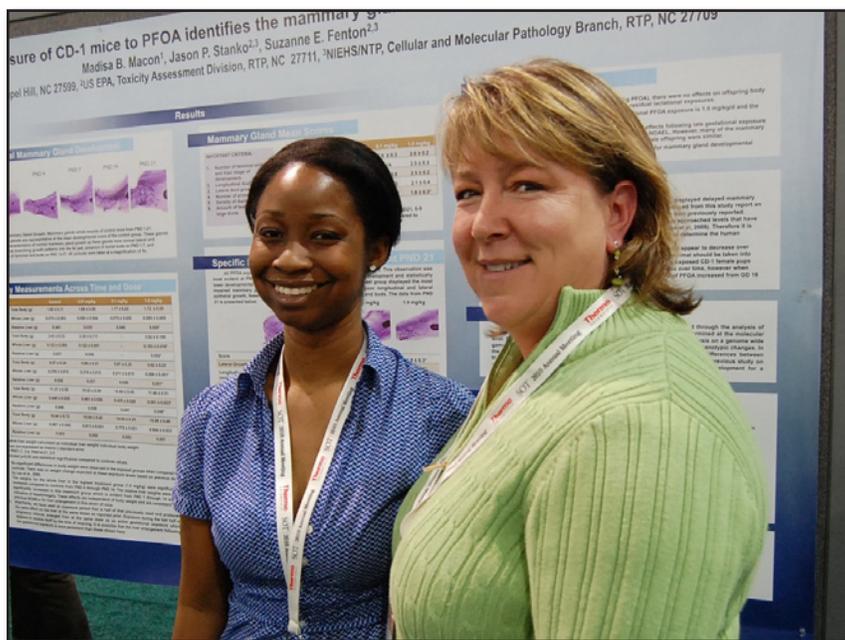
The [C8 Science Panel](#), organized to research the potential health effects of PFOA in industry-contaminated parts of West Virginia and Ohio, has determined that PFOA may have a probable link to kidney cancer, testicular cancer, ulcerative colitis, thyroid disease, hypercholesterolemia, and pregnancy-induced hypertension, including preeclampsia, in humans.

Research by Macon and her colleagues in Fenton’s group is making significant contributions toward understanding how exposure to PFOA, and other chemicals of interest, may also impact early life human development and lifelong health more subtly through modifications in gene expression triggered by low-dose exposures during critical windows of development.

in 2009 as a predoctoral fellow, as she pursued her Ph.D. from the UNC School of Medicine [Curriculum in Toxicology](#). Fenton is one of eight NIEHS lead researchers who serve as members of the curriculum, and currently serves on its executive committee.

In addition to her doctoral degree and award, Macon was first author on two peer-reviewed publications by Fenton's group. She has been active in the Society of Toxicology (SOT) nationally, and at the state level as a North Carolina Chapter representative. Her future plans include continuing as a postdoctoral fellow in the Tumor Biology Program at Georgetown University, as she works toward toxicology certifications, including the Diplomate of the American Board of Toxicology, and sharpens her career focus in the field of cancer.

“I am very grateful for the opportunities I’ve enjoyed at NIEHS and in the NTP Laboratory,” Macon said, “and I can’t say enough about how much Sue has helped me as mentor and advisor. I’m especially proud that UNC has recognized the public health impact of my work on PFOA, and I am grateful for Sue’s guidance during my research.”



*Macon's study of PFOA was selected as a 2011 NTP paper of the year. (Photo courtesy of Steve McCaw)*

*Fenton, right, joined Macon during a poster presentation at the Society of Toxicology annual meeting in March 2010. (Photo courtesy of Ed Kang)*

#### *Citations:*

[Macon MB](#), [Fenton SE](#). 2013. Endocrine disruptors and the breast: early life effects and later life disease. *J Mammary Gland Biol Neoplasia* 18(1):43-61.

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

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# Unexpected protein partnership has implications for cancer treatment

By Pamela Kidron

NIEHS scientists have identified two unlikely partners that may alter tumor growth by working together in response to cancer drugs to increase inflammation. Researchers from the Laboratory of Respiratory Biology (LRB) published the [study](#) in the journal *Cancer Research*.

These partners, located in a type of immune cell called a macrophage, are the p53 protein that suppresses tumors and the nuclear factor-kappaB (NF-kappaB) protein that stimulates their growth. Blocking this partnership could help prevent inflammation from occurring in cancer patients undergoing chemotherapy.

“Since many chemotherapy drugs target p53 to fight cancer cells, our finding helps us better understand the inflammatory-based side effects often seen in patients undergoing chemotherapy, as well as roles for inflammation within tumors,” said Julie Lowe, Ph.D., lead author on the paper and fellow in LRB.

## Proteins thought to have opposing roles

Both p53 and NF-kappaB have been studied in modern cancer research, but they were generally viewed as having opposite effects on growth. This study is among the first to show a cooperative interaction between p53 and NF-kappaB in human immune cells, and to reveal unexpected roles of p53 in tumor-related macrophages.

Researchers exposed immune cells from the blood and lungs of healthy volunteers at the NIEHS Clinical Research Unit to p53-activating chemotherapeutic drugs and then measured inflammatory response. They found that these drugs enhanced the expression of molecules that direct inflammation, an effect that required both p53 and NF-kappaB. The study also characterized a role for p53 in immune cells associated with tumors.

## Implications for both cancer and lung disease

Currently, most cancer therapies related to the p53 tumor suppression process are directed at activating the p53 protein. This study has clinical applications not only for cancer, but also for smoking-related lung disease, as smoking also activates p53. Modifying this pathway through inhibitors of p53 activation could decrease the inflammatory response, both in cancer treatment and in lung diseases such as chronic obstructive pulmonary disease.



*“The novelty of our study is that we show, in response to drugs used to treat cancer patients, p53 and NF-kappaB work together to promote inflammatory responses in cells central to the immune system,” noted Lowe. (Photo by Steve McCaw)*



*“This effort continues our extensive work on the human tumor suppressor p53, which is altered in over half of human cancers,” said Michael Resnick, Ph.D., lead researcher and head of the NIEHS Chromosome Stability Group. (Photo by Steve McCaw)*

*Citation:* Lowe JM, Menendez D, Bushel PR, Shatz M, Kirk EL, Troester MA, Garantziotis S, Fessler MB, Resnick MA. 2014. p53 and NF-kappaB coregulate proinflammatory gene responses in human macrophages. *Cancer Res.* 74(8):2182-2192.

(Pamela Kidron is a contract writer with the NIEHS office in Bethesda, Md.)

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## **Arsenic in well water may diminish intelligence in children**

*By Carol Kelly*

Evidence of a long-suspected connection between arsenic exposure and decreased intelligence among children is reported in a new study by NIEHS-funded scientists from Columbia University, published in the journal *Environmental Health*. Although the researchers conducted similar studies with children in Bangladesh, this [study](#) is the first of its kind in the U.S. to show an association between exposure to arsenic in drinking water and decreased intellectual function.

### **Alarming findings**

The findings suggest that levels of arsenic in drinking water equal to or greater than 5 parts per billion could pose a threat to a child's developing nervous system. This is a lower concentration than the U.S. Environmental Protection Agency (EPA) national standard of no more than 10 parts per billion, and is not uncommon in some U.S. regions.

Gail A. Wasserman, Ph.D., lead author of the study, noted that comparable effects of lead exposure on children's intelligence scores have been documented in recent years. "These findings call out for further replication in additional U.S. populations," she said.



*Wasserman is professor of medical psychology in the Department of Psychiatry at Columbia University. (Photo courtesy of Gail Wasserman)*

### **Measuring intellect and exposure**

Three school districts in Maine took part in the study, providing a sample of 272 children in grades 3 through 5. Researchers measured intelligence with the Wechsler Intelligence Scale for Children, Fourth Edition — the most commonly used assessment tool for children aged 6 to 16. They adjusted results for maternal intelligence and education, home environment characteristics, school district, and number of siblings in the home.

Participating families relied on household well water for drinking and cooking. Children in the sample had resided in their current homes an average of 7.3 years, ensuring they had the same home water source for much of their lifetimes. The researchers compared children with home water arsenic levels of 5 parts per billion or greater to those with lower home levels.

Children with the higher levels of arsenic in their home water supply showed reductions of 5-6 points in most aspects of intelligence.

## Translating knowledge into prevention

Arsenic, naturally present at high levels in groundwater in certain regions, poses serious health risks in addition to neurodevelopmental disruption, as explained in a recent peer-reviewed [article](#) on the health effects of arsenic. According to the review, arsenic is a carcinogen and has also been associated with cardiovascular disease and diabetes. It leaves no bodily system untouched, and early-life exposure may be related to increased risk for several diseases years or even decades after exposure. Where levels of arsenic in drinking water are high, the authors advise that the most important preventive action such communities can take to reduce the threat to public health is to limit further exposure by providing a safe water supply.

Testing water is vital, as are a family's efforts to mitigate arsenic exposure through the use of appropriate filtration systems, according to Wasserman. Follow up testing is also important, to monitor effectiveness of filtration systems.

*Citation:* Wasserman GA, Liu X, Lolocono NJ, Kline J, Factor-Litvak P, van Geen A, Mey JL, Levy D, Abramson R, Schwartz A, Graziano JH. 2014. A cross-sectional study of well water arsenic and child IQ in Maine schoolchildren. *Environ Health* 13 (1):23.



Joseph Graziano, Ph.D., is director of the Superfund Research Program at Columbia University and lead researcher on the arsenic study. (Photo courtesy Steve McCaw)



Some of the elementary school children in Maine who participated in the study. (Photo courtesy of Columbia University)

(Carol Kelly is a health and science writer with MDB, Inc., a contractor for the Division of Extramural Research and Training of NIEHS.)

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## Graziano honored by Society of Toxicology

Joseph Graziano, Ph.D. recently received the 2014 Career Achievement Award from the Metals Specialty Section of the Society of Toxicology.

This leadership and service award recognizes the depth and breadth of his scientific contributions to the field. It also acknowledges his guidance for young scientists and influence on regulatory and risk assessment related to metals toxicology. Graziano's research career is devoted to understanding the health and social consequences of exposure to metals, particularly lead, arsenic, and manganese, both on the molecular and population levels.

# NIEHS-funded researchers discover novel compound that could treat autoimmune diseases

By Sheila Yong

Patients with autoimmune disorders often experience painful side effects of the drugs they take to suppress their immune systems. Now, thanks to NIEHS-funded research, there may soon be a way to avoid these side effects.

In a [study](#) published Feb. 19 in the journal PLOS ONE, Nancy Kerkvliet, Ph.D., and Siva Kumar Kolluri, Ph.D., both professors at Oregon State University (OSU), report discovery of a chemical compound that may prevent the immune system of these patients from attacking their bodies, while sparing them from the side effects of currently available drugs. Although studies in human subjects are still required, this chemical may result in a safer alternative to treating autoimmune diseases.

## A targeted approach to taming the immune system

Autoimmune diseases can affect almost any part of the body, resulting in diseases such as colitis, multiple sclerosis, and psoriasis. For patients with these diseases, T cells — cells that normally protect the body from pathogens and infections — become hyperactive and attack tissues and organs.

By screening over 50,000 chemical compounds, [Kerkvliet](#) and [Kolluri](#) found that one chemical, known as 10-Cl-BBQ, binds to a protein inside the T cells called the aryl hydrocarbon receptor (AhR). The resulting chemical-protein complex then moves into the nucleus and turns on a gene expression process that converts the cells into regulatory T cells (Tregs), which suppressed the immune response.

The researchers then used 10-Cl-BBQ to treat mice with graft-versus-host disease — a condition in which the immune system tries to eliminate foreign cells. They found that treating these mice daily completely suppressed the disease. This observation suggests that 10-Cl-BBQ could also be used in patients who receive stem cell or bone marrow transplants to prevent graft rejection.

## Effect without apparent side-effect

“10-Cl-BBQ is different from other treatments used to suppress the immune system, because it acts directly in the T cells to turn them into regulatory T cells,” Kerkvliet said in an OSU [press release](#). Therefore, she believes that it will cause fewer side effects than currently used drugs. 10-Cl-BBQ is a member of the benzimidazoisoquinoline (BBQ) family, and further analysis of this family of chemicals revealed two other compounds that can induce regulatory T cell formation.

Frederick Miller, M.D., Ph.D., chief of the NIEHS Environmental Autoimmunity Group, believes that the findings from this study have immense therapeutic potential. “These interesting findings, based upon a large body of research implicating the AhR and its pathways as key modulators of inflammation, open up new approaches to the treatment of a wide variety of immune-mediated illnesses,” he commented. [Miller](#) said it is important to continue exploring the use of BBQ compounds as treatments for autoimmune disorders and inflammatory diseases, to determine candidates that are best suited for further drug development.



*Kerkvliet is a professor of immunotoxicology and deputy director of the Environmental Health Sciences Center in the OSU Department of Environmental and Molecular Toxicology. (Photo courtesy of Nancy Kerkvliet)*

## A surprise discovery from studying a harmful toxin

Kerkvliet has spent most of her career studying a notorious environmental contaminant known as TCDD, or 2,3,7,8-tetrachlorodibenzo-p-dioxin. Interestingly, at the cellular level, 10-Cl-BBQ functions like TCDD. However, unlike TCDD, 10-Cl-BBQ is rapidly broken down and eliminated by the body, which means it can stimulate regulatory T cell formation without harmful side effects. “We spent all these years studying TCDD, because people have been concerned about its presence in the environment,” Kerkvliet said. “Yet, look what we have now discovered from those basic toxicology studies.”

[Michael Humble, Ph.D.](#), NIEHS health scientist administrator who oversees the OSU grant, agrees. “Dr. Kerkvliet’s project is a wonderful example of how basic research into the action of a toxic substance can help us understand how a related, but less toxic, chemical may play a role in improving public health.”

*Citation:* [Punj S, Kopparapu P, Jang HS, Phillips JL, Pennington J, Rohlman D, O’Donnell E, Iversen PL, Kolluri SK, Kerkvliet NI.](#) 2014. Benzimidazoisoquinolines: a new class of rapidly metabolized aryl hydrocarbon receptor (AhR) ligands that induce AhR-dependent Tregs and prevent murine graft-versus-host disease. *PLoS One* 9(2):e88726. [Summary](#)

(Sheila Yong, Ph.D., is a visiting fellow in the NIEHS Inositol Signaling Group.)

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## Core Day highlights resources available to NIEHS researchers

*By Aleksandra Adomas*

Each year, Core Day brings together support organizations within NIEHS to highlight their resources and provide information to potential Institute users. This year’s event, held April 7 in Rodbell Auditorium, was organized by Bob Petrovich, Ph.D., head of the Protein Expression Core. During the course of the event, more than 125 researchers talked to presenters of 34 posters from 18 different support groups. A slide show rolling in the background provided attendees with additional details on each group.

The core facilities are a unique resource available to NIEHS researchers. They handle routine tasks involving a high number of samples, such as genotyping or DNA sequencing; provide support with experiments requiring specialized technical skills, such as performing microarray hybridization or creating a specialized breed of mouse; offer expertise in less common specialties, such as data analysis, pathology, or clinical research; and provide access to expensive and state-of-the-art equipment, including flow cytometry, confocal microscopy, and mass spectrometry.

An information scavenger hunt encouraged Core Day participants to talk to poster presenters and gather their signatures.



*Kolluri, a cancer biologist at Oregon State University, has studied other substances that bind to the AhR protein, recently finding AhR to be a potential target for drug development in liver and stubborn breast cancers (see [story](#)). (Photo courtesy of Nancy Kerkvliet)*

## NIEHS Core Facilities

**Integrative Bioinformatics** supports the management and analyses of large genomic datasets, such as those derived from Next Generation (NextGen) sequencing platforms, including those generated by the Epigenomics Core.

The **Epigenomics Core** provides NextGen sequencing capacity with Illumina MiSeq and manages a Sanger sequencing contract with Genewiz Inc.

The **Molecular Genomics Core** includes:

- The **Microarray Group**, which offers multiple microarray platforms for DNA methylation, ChIP-chip, comparative genomic hybridization, and single nucleotide polymorphism analysis.
- The **Genotyping Group**, which handles mouse tail genotyping.

**Microarray and Genome Informatics** specializes in data mining and computational data analysis for array-based platforms, NextGen sequencing, genomic scanning, and gene expression coregulation. It includes bioinformaticians, computational biologists, and scientific programmers from the Biostatistics Branch, Microarray Group, and Integrative Bioinformatics Group.

The **Flow Cytometry Center** offers fluorescent-activated cell sorting and analysis.

The **Fluorescence Microscopy and Imaging Center** provides access to state-of-the-art microscopy techniques, image analysis protocols, and tools.

The **Protein Expression Core Facility** assists NIEHS investigators with their protein expression requirements and specializes in production of heterologous proteins in *E. coli*, insect cells, and mammalian cells.

The **Protein Microcharacterization Core Facility** provides cutting-edge mass spectrometry services, including protein identification and characterization of post-translational protein modifications.

The **Collaborative Mass Spectrometry Group** specializes in characterizing proteins, quantifying changes in protein abundance in cells and animals upon exposure to external factors, and identifying and quantifying small molecules.

The **Collaborative X-ray Crystallography Group** manages instruments necessary for structural determinations using X-ray crystallography.

The **Computational Chemistry Molecular Modeling Support Group** assists investigators with structural alignments, docking, modeling, energetics, and graphics visualizations.

The **Knockout Core** can generate a mutant mouse customized to research needs, including traditional knockouts, conditional knockouts, and knockins.

## NIEHS Core Facilities (cont'd)

The **Comparative Medicine Branch** is in charge of animal resources:

- The **Quality Assurance Laboratory** oversees detection, isolation, and elimination of pathogenic, microbial, and chemical contaminants.
- **Veterinary Medicine** offers training and assistance in rodent imaging, rodent behavior phenotyping, animal health oversight, surgery, anesthetic selection, and animal study development.

The **Pathology Support Core Facilities** provide diagnostic pathology support and includes:

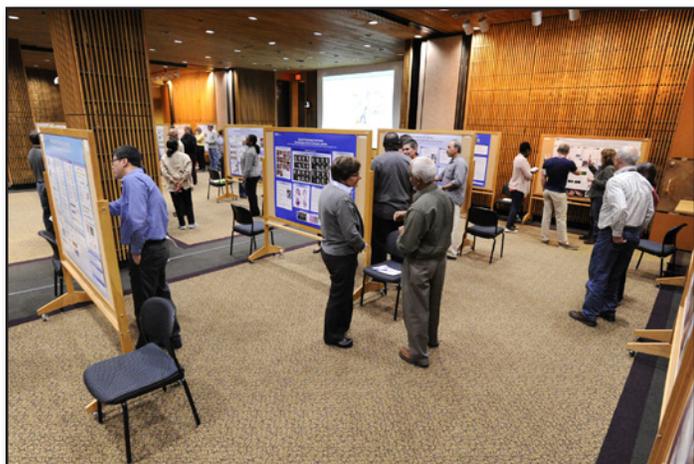
- The **Histology Group**, specializing in immunohistochemistry, electron microscopy, and necropsy.
- The **Special Techniques Laboratory**, which handles mouse phenotyping, laser microdissection, digital image analysis, and graphics.
- The **Clinical Pathology Group**, which handles clinical chemistry and hematology.

## Scientific Resources

The **Clinical Research Unit** is a resource for collaborative, translational research involving basic and clinical science.

- The **Clinical Research Unit Laboratory** handles human biospecimen and clinical sample testing.
- The **Environmental Polymorphisms Registry** contains blood samples from over 18,000 participants in North Carolina, and is a resource for studying rare disease variants.

The **Library** offers training classes, including data management training, and assists with literature searches, access to electronic journals, and book rentals.



*Core facilities make tremendous contributions to the work done by intramural researchers, by performing experiments and also offering expert advice on experimental design and data analysis. (Photo courtesy of Steve McCaw)*



*Core Day was an opportunity for representatives from different groups to get better acquainted with what the support facilities have to offer. Hong Xu, right, of the Molecular Genomics Core, engages with contract bioinformatician Xiaojiang Xu. According to Hong Xu, the Molecular Genomics Core ran 70,000 genotypes last year. (Photo courtesy of Steve McCaw)*



*Pamela Ovwigho, right, shows NIEHS Deputy Director Rick Woychik, Ph.D., examples of tissue staining the histology group can provide. (Photo courtesy of Steve McCaw)*



*Kathy Laber, D.V.M., center, of the Comparative Medicine Branch, explains operations in the NIEHS animal care and use program. (Photo courtesy of Steve McCaw)*



*The Fluorescence Microscopy and Imaging Center, led by Jeff Tucker, left, is one of the most-used cores, with over 200 active users from 49 different laboratories at the Institute. (Photo courtesy of Steve McCaw)*



*Lalith Perera, Ph.D., right, head of the Computational Chemistry Molecular Modeling Support Group, explained that while protein crystal structures are static, quantum dynamics can provide insights into what happens when an enzyme undergoes reorganization. (Photo courtesy of Steve McCaw)*

(Aleksandra Adomas, Ph.D, is a former research fellow in the NIEHS Laboratory of Molecular Carcinogenesis.)

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## Exposure science in the 21st century

By Annah Wyss

Paul Lioy, Ph.D., professor of environmental and occupational medicine at Rutgers University, shared his vision for exposure science in the 21st century, during an April 3 seminar co-hosted by NIEHS and the U.S. Environmental Protection Agency (EPA). The talk was held on the EPA campus in Research Triangle Park, N.C. Using a National Research Council [report](#) on exposure science as a foundation for his talk, Lioy stressed the need for collaboration across environmental health fields, to deliver knowledge that is effective, timely, and improves health.

## From external sources to internal doses

In outlining the goals of exposure science, Lioy first emphasized the need to examine the link between external exposure and the resulting internal doses. He highlighted several tools that have enhanced efforts to accomplish this goal in recent years, including use of biomarkers; evaluation of source-exposure and source-disease relationships; consideration of the exposome — a measure of lifetime exposures, both internal and external; development of comprehensive exposure datasets; and incorporation of a systems approach.

“Exposure science examines intensity and duration of the contact of humans or other organisms with agents, and the relationship to health,” Lioy explained.

To demonstrate the value of developing comprehensive exposure datasets, he described his group’s work to establish a user-friendly system, known as NJ Risk, which will query existing national and international databases for chemicals both old and new. The system, designed by [Panos Georgopoulos, Ph.D.](#), also at Rutgers, will then estimate exposures, in order to computationally characterize the associated health risks.

## Goals and applications

In addition to better characterizing internal doses resulting from exposures to external sources, Lioy identified the goals of exposure science as encompassing the identification of multiple levels of exposure and interactions between multiple stressors, exploring exposures in conjunction with lifestyle and behavioral factors, and scaling research from molecular systems to individuals to vulnerable populations to ecosystems.

“We need to understand time, activity, and behavior better,” he said, with respect to exposures to substances such as environmental toxins. Though useful, most available data sets were collected before 2000, and do not capture changes in lifestyle that have occurred in the 21st century, such as the prevalence of cell phone use.

To better estimate exposure, Lioy said that investigators must track both existing and emerging chemicals, characterize the health effects of low-level stressors, rapidly respond to natural and human-caused disasters, and maintain local and global environments, by identifying and controlling potential health hazards.

## Expansion and integration

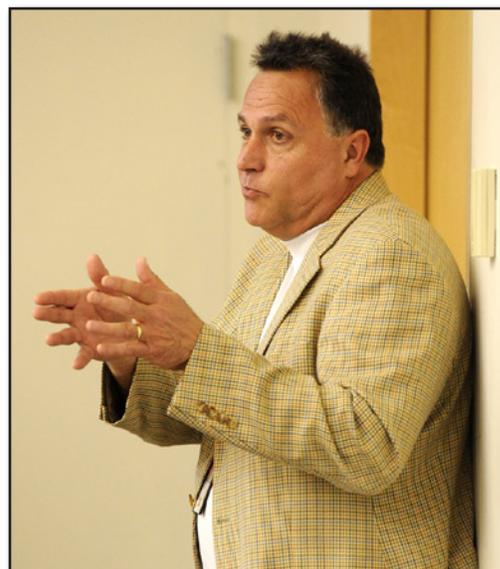
Lioy closed by outlining three new opportunities to expand and integrate exposure science — the exposome, the microbiome, and precision environmental health, which focuses on exposures at the individual level. “Integration within environmental health will lead toward a focus on individual health,” Lioy concluded.

(Annah Wyss, Ph.D., is a research fellow with the NIEHS Genetics, Environment, and Respiratory Disease Group.)

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*Lioy is an expert in the field of exposure science and has researched a wide range of air pollutants. He recently served as vice chair of the National Research Council Committee on Human and Environmental Exposure Science in the 21st Century. (Photo courtesy of Steve McCaw)*



*Daniel Vallero, Ph.D., environmental scientist with EPA, hosted Lioy and moderated the question-and-answer session. (Photo courtesy of Steve McCaw)*

## Chris Weis elected to ABT board of directors

*By Kelly Lenox*

Among the flurry of seminars, exhibits, networking, and associated activities at the March Society of Toxicology (SOT) meeting (see [story](#)), came an extra honor for NIEHS toxicology liaison Christopher Weis, Ph.D. In recognition of his expertise and experience in toxicology, the American Board of Toxicology announced the election of Weis to its board of directors.

“I’m very pleased to see Chris recognized for the valuable contribution he can make at ABT,” said NIEHS and NTP Director Linda Birnbaum, Ph.D., a diplomate of ABT (DABT). Although Weis is serving in a personal capacity, rather than as a representative of NIEHS, his position as senior advisor to Birnbaum provides him a perspective that will be important in his role implementing standards for DABT eligibility and certification.

“I will work with other members to maintain and improve professional requirements for my colleagues who work in the field of toxicology and those who seek certification or recertification,” explained Weis.

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*At the recent SOT meeting in Phoenix, Weis engaged with colleagues he has formed nationally and internationally in his role as NIEHS toxicology advisor. (Photo courtesy of Steve McCaw)*

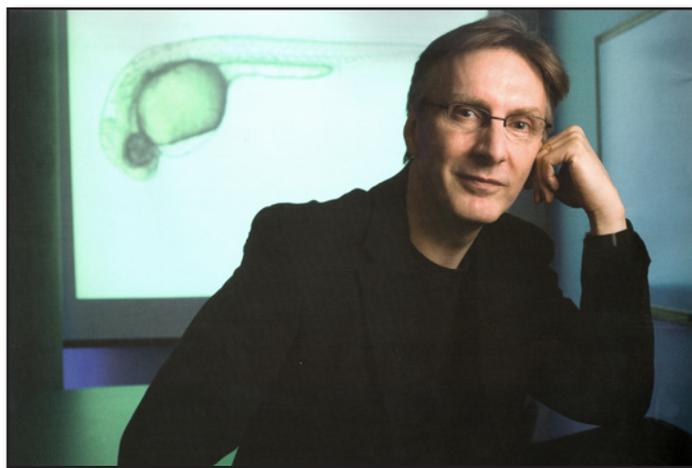
## Distinguished Lecture Series to welcome Christopher Wright, Ph.D.

*By Monica Frazier*

The NIEHS Distinguished Lecture Series will present Christopher Wright, D.Phil., of Vanderbilt University School of Medicine, May 6 at 11:00 a.m. in Rodbell Auditorium. The lecture will be hosted by Anton Jetten, Ph.D., head of the NIEHS Laboratory of Respiratory Biology.

Wright bears an impressive number of titles, including director of the Vanderbilt University Program in Developmental Biology, as well as professor and vice-chair of faculty affairs in the same program. In addition, he is the Louise B. McGavock Chair of Cell and Developmental Biology.

Wright’s [laboratory](#) includes graduate students and postdoctoral fellows studying early embryonic development and the role that intercellular signaling molecules, known as transcription factors, play in dictating cell fates in different parts of the embryo.



*After his May 6 lecture, Wright will join NIEHS fellows for lunch and informal discussion. (Photo courtesy Vanderbilt University)*

The title of his lecture, “Reprogramming Within the Pancreas and Endoderm: Biological-Therapeutic Connections,” reflects his research group’s focus on finding methods to convert stem cells into pancreatic tissue for use in diabetes therapy. Using frog, zebrafish, and mice embryos, Wright and his colleagues are making great progress in this area.

After the seminar, NIEHS fellows will have the opportunity to have lunch with Wright. Organized by postdoctoral fellow and [NIEHS Trainees Assembly](#) steering committee member Sabrina Robertson, Ph.D., these lunches are a great opportunity for networking, and give NIEHS fellows a chance to learn more about lecturers and their career paths, as well as discuss scientific and career development issues. The variety of roles Wright plays at Vanderbilt make him a great resource for fellows interested in multiple career paths.

(Monica Frazier, Ph.D., is an Intramural Research Training Award fellow in the NIEHS Mechanisms of Mutation Group.)

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## This month in EHP

The May issue of Environmental Health Perspectives ([EHP](#)) focuses attention on the emerging One Health movement and growing concern — and controversy — over low-level exposures to arsenic.

### Seeing the Forest for the Trees: How “One Health” Connects Humans, Animals, and Ecosystems

The One Health movement explicitly recognizes the inextricable connections between human, animal, and ecosystem health. This heightened awareness is leading to new scientific research and projects that help people rise out of poverty, improve their health, reduce conflicts with wildlife, and preserve ecosystems.

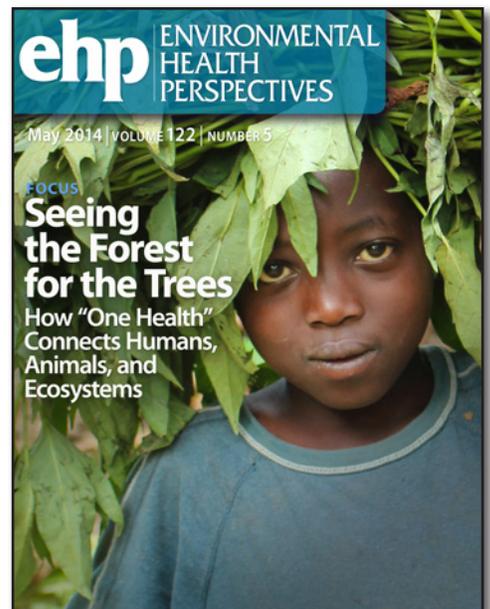
### Low-Dose Arsenic: In Search of a Threshold

Many researchers increasingly believe exposure to harmful levels of arsenic may be more widespread than previously recognized. Protecting against low-level exposure is challenging, given that arsenic is a natural element in the Earth’s crust and is widespread in the environment.

Moreover, the evidence for low-dose effects is controversial. This disagreement is a problem for regulators who face mounting pressure to re-evaluate standards for arsenic.



<http://twitter.com/ehponline>



## Featured research and related news articles this month include:

- **Environmental Burden of Disease in Europe: Assessing Nine Risk Factors in Six Countries** — Shared Burden: Public Health Impact of Nine Environmental Pollutants in Europe
- **Gestational Exposure to Endocrine-Disrupting Chemicals and Reciprocal Social, Repetitive, and Stereotypic Behaviors in 4- and 5-Year-Old Children: The HOME Study** — Clues to Autistic Behaviors: Exploring the Role of Endocrine Disruptors
- **Standardizing Benchmark Dose Calculations to Improve Science-Based Decisions in Human Health Assessments** — New Confidence: Optimizing Benchmark Dose Modeling to Improve Risk Assessments
- **Estimating the Health Effects of Greenhouse Gas Mitigation Strategies: Addressing Parametric, Model, and Valuation Challenges** — Climate Change Mitigation: Assessing Strategies That Offer Potential Human Health Benefits

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## Extramural papers of the month

*By Nancy Lamontagne*

- [Silicone wristbands as personal passive samplers](#)
- [Exposure to bisphenol A linked with early-onset prostate cancer](#)
- [Possible new autoimmune disease treatment without side effects](#)
- [Methylation in the adult mammalian brain](#)



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

## Silicone wristbands as personal passive samplers

NIEHS-funded investigators report that commercially available silicone wristbands could be modified for use as a personal passive sampling device, turning them into a valuable and easy-to-use tool for determining individual exposures.

Before deployment, materials that might interfere with future chemical analyses were reduced with various solvents. The researchers then developed a way to extract and analyze an unprecedented number of chemical compounds from the silicone wristbands after they are worn. To test the process, they provided 38 volunteers, eight of whom were roofers, with wristbands. After wearing them during day-to-day activities for 30 days, the volunteers placed their wristbands in a Teflon bag and sent them to the researchers for analyses. The scientists identified 49 different absorbed substances, including polycyclic aromatic hydrocarbons (PAHs), flame retardants, and compounds from pesticides and consumer products. They detected absorbed PAHs, including 12 on a federal priority list of harmful pollutants, in all of the roofers' wristbands.

The test revealed that the wristbands are easy to use, that people will wear them, and that they had very good analytical sensitivity. The researchers say they can screen for, and quantify, over 1,000 chemicals that may accumulate in the wristbands, including PCBs, industrial chemicals, and consumer and pharmaceutical products.

*Citation:* O'Connell SG, Kincl LD, Anderson KA. 2014. Silicone wristbands as personal passive samplers. *Environ Sci Technol* 48(6):3327-3335. [[Story](#)]

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## Exposure to bisphenol A linked with early-onset prostate cancer

In an NIEHS-supported study, researchers found that men with prostate cancer had higher urinary levels of bisphenol A (BPA), suggesting that urinary BPA level is an independent prognostic marker of prostate cancer. Scientists also report new information about a possible mechanism for the BPA influence in transformation of prostate cells into cancer cells.

The researchers examined urine BPA levels in 60 urology patients and found that prostate cancer patients had higher levels of BPA, 5.74 micrograms per gram (95 percent confidence interval; 2.63, 12.51) than patients without prostate cancer, 1.43 micrograms/gram (95 percent confidence interval; 0.70, 2.88) ( $p = 0.012$ ). The difference in BPA levels was even more significant in patients who were younger than 65.

They also examined how prostate cancer cells and normal prostate cells responded to low doses of BPA. For both types of cells, BPA exposure increased the percentage of cells with more than the normal number of centrosomes two-fold to eight-fold, and also induced other cellular changes. These findings suggest low-dose BPA may lead to the development of prostate cancer, by disrupting centrosome duplication.

*Citation:* Tarapore P, Ying J, Ouyang B, Burke B, Bracken B, Ho SM. 2014. Exposure to bisphenol A correlates with early-onset prostate cancer and promotes centrosome amplification and anchorage-independent growth in vitro. *PLoS One* 9(3):e90332. [[Story](#)]

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## Possible new autoimmune disease treatment without side effects

NIEHS grantees have discovered a compound that may be a safer alternative for treating autoimmune diseases. The compound works differently than currently used drugs, and the researchers think that it will likely have fewer side effects.

In previous work, the researchers had discovered that the toxic environmental contaminant 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) suppressed the immune system by targeting the aryl hydrocarbon receptor (AhR) in T cells. The researchers used this knowledge to screen for compounds that activated AhR, without harming cells, identifying 10-chloro-7H-benzimidazo[2,1-a]benzo[de]Iso-quinolin-7-one (10-Cl-BBQ) as a candidate. Further analysis showed that 10-Cl-BBQ binds to AhR inside T cells and changes the cells into regulatory T cells, which suppress the immune response.

The researchers tested 10-Cl-BBQ in mice with graft-versus-host disease, a condition in which the immune system tries to eliminate foreign cells. Daily injections of 10-Cl-BBQ completely suppressed the disease. The compound was rapidly metabolized and excreted, and was not toxic at the dosage used, making it a potential candidate for drug development.

*Citation:* Punj S, Kopparapu P, Jang HS, Phillips JL, Pennington J, Rohlman D, O'Donnell E, Iversen PL, Kolluri SK, Kerkvliet NI. 2014. Benzimidazoisoquinolines: a new class of rapidly metabolized aryl hydrocarbon receptor (AhR) ligands that induce AhR-dependent Tregs and prevent murine graft-versus-host disease. PLoS One 9(2):e88726. [[Story](#)]

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## Methylation in the adult mammalian brain

Research, funded in part by NIEHS, reveals new information about an epigenetic mechanism that regulates gene expression in the mouse brain. This mechanism may contribute to the neurodevelopmental disorder Rett syndrome and other neurological disorders.

Epigenetic changes, such as DNA methylation, control gene expression without changing DNA code. Historically, scientists believed methyl groups could only attach to a cytosine followed by a guanine (CpG). But in recent years, methyl groups have been found on other sequences. In the new work, the researchers conducted systematic analyses of DNA methylation in the adult mouse brain with single-base resolution, and also mapped genomic distribution.

They found that adult mouse neurons have both non-CpG and CpG methylation. They observed non-CpG methylation in DNA regions lacking CpG methylation, meaning that it can likely control gene expression independently of CpG methylation. Additional experiments showed that non-CpG methylation occurs postnatally, is dynamic, and can repress gene expression. They also found that non-CpG methylation and CpG methylation are both read by the methyl-CpG binding protein 2 (MeCP2 enzyme), which is important because MeCP2 mutations lead to problems in neural development and neuronal functions, and are also linked to the neurodevelopmental disorder Rett syndrome.

*Citation:* Guo JU, Su Y, Shin JH, Shin J, Li H, Xie B, Zhong C, Hu S, Le T, Fan G, Zhu H, Chang Q, Gao Y, Ming GL, Song H. 2014. Distribution, recognition and regulation of non-CpG methylation in the adult mammalian brain. Nat Neurosci 17(2):215-222.

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

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## Intramural papers of the month

*By Kimberly Cannady, Kristin Lichti-Kaiser, Zachary McCaw, and Staton Wade*

- [Risk factor for lung disease in premature infants](#)
- [A fresh look at the genetics of breast cancer](#)
- [Humans with APOE4 gene more prone to inflammation](#)
- [Regulation of alternative polyadenylation is required for ESC self-renewal](#)

## Risk factor for lung disease in premature infants

NIEHS scientists and their colleagues have identified a gene known as *Chrm2* that may make premature infants susceptible to a chronic lung disease called bronchopulmonary dysplasia (BPD).

Following up on previous studies that unveiled a genetic component to BPD, researchers exposed neonatal mice to either supplemental oxygen or room air (control group). The mice that were exposed to supplemental oxygen sustained more lung inflammation than the control group, but the severity of the damage varied depending on the genetic background of each mouse. Using a statistical technique called genome-wide association mapping, researchers identified chromosomal regions containing genetic sequence differences that could account for the differential responses.

*Chrm2* was among the candidate genes identified. They found that mice with a functional mutation in the *Chrm2* gene, which codes for receptors that contribute to a certain type of airway inflammation, experienced less lung injury and inflammation. Because this damage is similar to the respiratory injury seen in human BPD, the researchers may be able to use *Chrm2* both as a therapeutic target to prevent neonatal lung injury and as a way to identify individuals at risk of developing BPD. **(ZM)**

*Citation:* Nichols JL, Gladwell W, Verhein KC, Cho HY, Wess J, Suzuki O, Wiltshire T, Kleeberger SR. 2014. Genome-wide associated mapping of acute lung injury in neonatal inbred mice. *FASEB J*; doi:10.1096/fj.13-247221 [Online 26 February 2014].

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## A fresh look at the genetics of breast cancer

Analyzing data from the NIEHS Sister Study, NIEHS scientists have found evidence suggesting that breast cancer risk is influenced by nonstandard genetic mechanisms. The [Sister Study](#) is a cohort of more than 50,000 sisters of women who have had breast cancer. The study, published in the journal *PLOS Genetics*, is the first to broadly assess possible contributions of understudied genetic mechanisms to the risk of breast cancer.

Genome-wide association studies have largely overlooked certain genetic mechanisms. For example, the maternal genome can act prenatally, the effect of a gene variant can depend on the parent of origin, and mitochondrial variants can influence risk. Because these mechanisms produce asymmetry in family histories of breast cancer, the scientists analyzed Sister Study data to compare rates in maternal versus paternal grandmothers. Significantly more maternal grandmothers than paternal grandmothers had developed breast cancer.

Using algebraic formulae, the researchers quantified the contributions of the nonstandard mechanisms to the asymmetry and showed that the small difference observed between maternal and paternal lineages could arise from a single nonstandard mechanism with a large effect. Ongoing analyses using families in the [Two Sister Study](#), an offshoot of the Sister Study, may be able to pinpoint the nonstandard mechanisms more directly. **(KC)**

*Citation:* Weinberg CR, Shi M, Deroo LA, Taylor JA, Sandler DP, Umbach DM. 2014. Asymmetry in family history implicates nonstandard genetic mechanisms: application to the genetics of breast cancer. *PLoS Genet* 10(3):e1004174.

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## Humans with APOE4 gene more prone to inflammation

NIEHS scientists and their colleagues are the first to report that people with a particular form of the lipid-regulating gene apolipoprotein E (APOE) — specifically the APOE4 allele — may be more prone to inflammation than others. Their findings were published in the *Journal of Allergy and Clinical Immunology*.

The researchers used the NIEHS [Environmental Polymorphisms Registry](#) to identify healthy volunteers, based on their APOE genotype. Using the NIEHS Clinical Research Unit to obtain and examine the samples, they found that whole blood from patients with at least one copy of APOE4 produced a more robust inflammatory response to lipopolysaccharide (LPS), a surface component of bacteria, than blood from patients who didn't express APOE4. Intravenous injection of LPS into another group of volunteers showed that those with APOE4 had a higher fever and inflammatory response than those without APOE4. Similarly, mice genetically engineered to express human APOE4 were injected with LPS and exhibited an enhanced inflammatory response. Finally, the researchers also found that APOE4 was associated with increased illness severity and coagulation system failure in patients with sepsis, a dysregulated innate immune response to infection.

APOE4 has been previously associated with the development of inflammatory diseases, such as cardiovascular disease and Alzheimer's. These findings indicate that APOE4 may contribute to the inflammatory disease process through its regulation of the innate immune response. **(KLK)**

*Citation:* Gale SC, Gao L, Mikacenic C, Coyle SM, Rafaels N, Murray Dudenkov T, Madenspacher JH, Draper DW, Ge W, Aloor JJ, Azzam KM, Lai L, Blackshear PJ, Calvano SE, Barnes KC, Lowry SF, Corbett S, Wurfel MM, Fessler MB. 2014. APOepsilon4 is associated with enhanced in vivo innate immune responses in human subjects. *J Allergy Clin Immunol*; doi:10.1016/j.jaci.2014.01.032 [Online 18 March 2014]. [[Story](#)]

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## Regulation of alternative polyadenylation is required for ESC self-renewal

NIEHS researchers and their collaborators have described a novel regulatory mechanism that explains how cells choose between multiple sites at the end of a gene for transcriptional termination, a process known as alternative polyadenylation (APA). APA is known to occur during development and carcinogenesis, and in response to environmental factors. However, this work provides the first evidence that APA regulation is critical for embryonic stem cell (ESC) self-renewal and cell fate decisions.

The scientists discovered that Fip1, a 3' mRNA processing factor, is required for ESC self-renewal and somatic cell reprogramming. Direct RNA sequencing, a technique that maps polyadenylation sites (PASs) at the 3' end of transcripts, demonstrated that Fip1 depletion alters the APA profiles of 374 genes in ESCs. Furthermore, Fip1 depletion resulted in transcripts with longer 3' untranslated regions and repressed the protein expression of many genes involved in self-renewal.

Mechanistically, the authors demonstrated that high levels of Fip1 in ESCs promote the usage of weaker, gene-proximal PASs, and that this effect is dependent on the distance between the alternative PASs of a given gene. Conversely, Fip1 repression during differentiation promotes distal PAS usage. The authors speculate that similar mechanisms may regulate APA changes during oncogenesis and embryonic development. **(SW)**

*Citation:* Lackford B, Yao C, Charles GM, Weng L, Zheng X, Choi EA, Xie X, Wan J, Xing Y, Freudenberg JM, Yang P, Jothi R, Hu G, Shi Y. 2014. Fip1 regulates mRNA alternative polyadenylation to promote stem cell self-renewal. EMBO J 33(8):878-889.

(Kimberly Cannady, Ph.D., is an Intramural Research Training Award (IRTA) fellow in the NIEHS Chromatin and Gene Expression Group. Kristin Lichti-Kaiser, Ph.D., is an IRTA fellow in the NIEHS Cell Biology Group. Zachary McCaw is a postbaccalaureate IRTA fellow in the NIEHS Environmental Genetics Group. Staton Wade, Ph.D., is an IRTA fellow in the NIEHS Chromatin and Gene Expression Group.)

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# Inside the Institute

## Discovery Lake gets a spring-cleaning

By Allison Ashley

Eight NIEHS volunteers arrived at Discovery Lake March 27 to clean the shoreline for the many plant and animal species that call it home. Participants, organized by the Environmental Awareness Advisory Committee and volunteers from the lake management group, focused on picking up fishing debris and other items that don't belong in or around the lake. Discovery Lake sits between NIEHS and the U.S. Environmental Protection Agency in Research Triangle Park, N.C.

The Health and Safety Branch (HSB) provided gloves and trash bags, and participants supplied their own outdoor gear for the job. Ken Coffey, Steve McCaw, Paul Johnson, Claire Long, Vee Vee Shropshire, Caranza Smith, and Bill Willis joined Bill Steinmetz, HSB environmental protection specialist, in the effort.

### Improved conditions over past years

“The area was a little cleaner this year,” said Steinmetz. “The lake is in pretty good shape. Everybody does a decent job of putting their waste where it needs to go, and the landscapers do a good job keeping the cleared fishing areas clean.” The small amount of trash collected during the cleanup was discovered away from the trails and appeared to have been there for some time.

A few years ago, an aquatic weed, *Ludwigia peploides* ssp. *Glabrescens*, also known as floating primrose, grew along the shoreline, extending 8-12 feet into the water and threatening to spread further. Lake monitors discovered that carp, which eat the vegetation, could no longer be found. In March and May of 2012, the lake was restocked with 150 carp, and they now, in combination with other aquatic and biological factors, help maintain the health of the lake and its habitants.

Discovery Lake is a popular location for employees who want to enjoy the walking trail along the shore, or bring family and guests for some fishing. Use of the clearly marked trash receptacles by lake visitors could make future spring cleanings unnecessary. With help from employees and visitors, the lake will continue to be a healthful habitat for fish and other living species.

(Allison Ashley is a program specialist in the NIEHS Office of Communications and Public Liaison.)



*Geese often walk freely among the lake's visitors. (Photo courtesy of Steve McCaw)*



*Steinmetz, left, uses a stick to pick up debris, while Johnson, hazardous waste program manager, assists him. (Photo courtesy of Steve McCaw)*



Many of the trails were free of litter this year, but there was still plenty for volunteers to pick up. (Photo courtesy of Steve McCaw)



Posing with her gloves, Long, of the Office of Management, was ready to clean up the shore. (Photo courtesy of Claire Long)



Willis and Coffey removed even small pieces of debris from around the lake. (Photo courtesy of Claire Long)



The weather cooperated, providing volunteers with a clear day for the cleanup. (Photo courtesy of Steve McCaw)

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## **Invasive-pest specialist enlightens NIEHS in Earth Week lecture**

*By Kelly Lenox*

As part of Earth Week at NIEHS, the Environmental Awareness Advisory Committee (EAAC) sponsored an enlightening discussion April 24 by entomologist Alonzo Suazo, Ph.D., on invasive species threatening North Carolina's varied ecosystems.

**Suazo**, with the North Carolina Department of Agriculture and Consumer Services (NCDACS), educated the audience on measures to halt the spread of several species. NIEHS hazardous waste manager and co-chair of EAAC Paul Johnson hosted Suazo's presentation.

Suazo was careful to distinguish between non-indigenous species, which include everything from corn and wheat to dogs and cats, and invasive species, which can damage ecosystems or agricultural crops. “The cost of damage was recently estimated at nearly \$200 billion per year, nationally,” Suazo said.

### Start with prevention

Scientists and government agencies have a variety of tools at their disposal to combat invasive pests, but the most effective action is prevention, Suazo emphasized. To that end, he shared a surprising vector by which invasive pests spread across the land — firewood.

According to Suazo, the natural spread of the highly destructive emerald ash borer (EAB), whose metallic green image graced the fliers for Suazo’s talk, is about 5 miles per year. However, in little over a decade it spread from Michigan to 20 states and two provinces of Canada. Scientists believe the EAB spread so rapidly via firewood transport — whether commercial or informal, among family and friends. Firewood is such an important means of travel that the NCDACS prepared a series of [fact sheets](#) on pests of current concern and telltale signs of firewood infestation.

### Available tools to combat invasive insects

Once an invasive species is detected, the race is on to survey the extent, limit the spread, and work to eradicate the pest. Surveys may include traps — for example, some insects can be lured to traps baited with pheromones. Visual inspection is useful for weeds and insects on which pheromones have no effect. It’s also the tool of choice for detecting the giant East African snail — “giant” is part of the official name, as it can grow up to 8 inches in length. According to Suazo, the species, imported illegally as a pet, currently devours plants in the Wilmington, N.C., area.

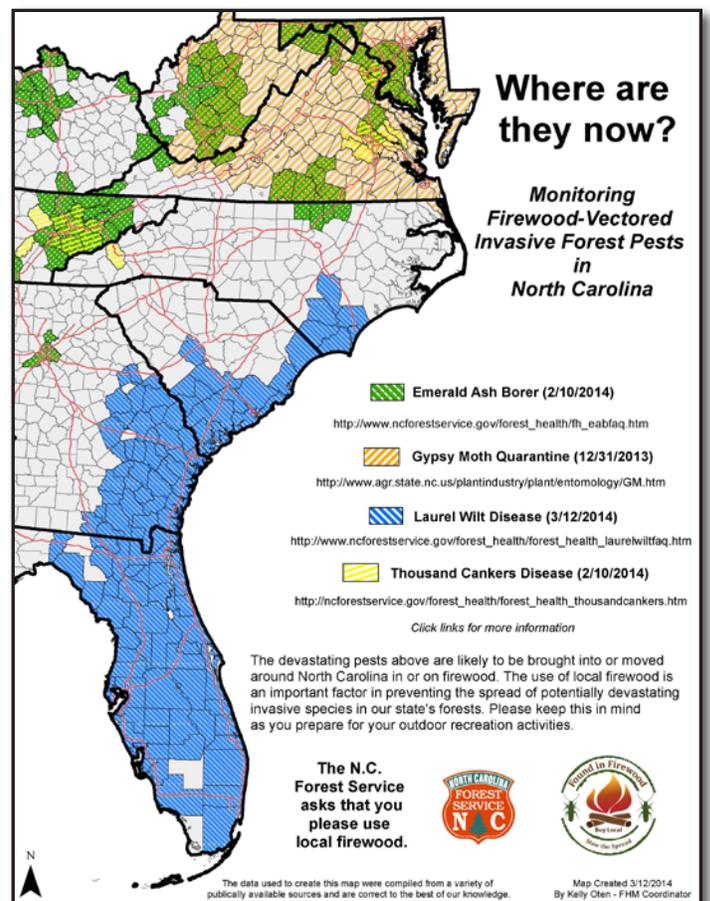
Another tool researchers use is biosurveillance — for example, the non-stinging *Cerceris fumipennis* wasp preys on the EAB. Researchers can determine whether the EAB has spread to a particular area by monitoring nests of this wasp for EAB remains.

Another effective approach is education and outreach, which was precisely Suazo’s mission with the alert and engaged audience at NIEHS. Suazo provided detailed, helpful answers to questions throughout his talk, and those who attended will likely be more careful where they buy their next load of firewood.

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Suazo explained that the gypsy moth travels by laying egg masses on cars, boats, and tents. The high numbers trapped around a particular rest stop in New Hanover County, N.C., are probably due to the boat repair facility across the street, he said. (Photo courtesy Steve McCaw)





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