

April 2015

NIEHS Spotlight



[IOM workshop examines role of environmental exposures in obesity epidemic](#)

The Institute of Medicine workshop March 2-3 explored research that is reshaping our understanding of the complex roots of obesity.



[Council meeting delayed by snow is productive](#)

The National Advisory Environmental Health Sciences Council approved concepts in children's health, Ebola worker training, nanotechnology, and cookstoves.



[NIEHS joins meeting of Prince Charles' foundation on health care and climate change](#)

John Balbus, M.D., joined the Feb. 25 discussions on ways the international healthcare community can respond to health risks posed by climate change.



[Toxicology and public health merge at SOT conference in San Diego](#)

NIEHS and NTP scientists joined thousands at the 2015 Society of Toxicology conference, discussing cutting-edge research and the NIH grants process.



[Valantine delivers inspiring 2015 Spirit Lecture](#)

Hannah Valantine, M.D., the inaugural NIH Chief Officer for Scientific Workforce Diversity, inspired listeners at the NIEHS Spirit Lecture March 10.

Clinical Feature



[New NHALES study will help asthma sufferers](#)

People with moderate to severe asthma can receive free treatment and medications by joining a new health study at the NIEHS Clinical Research Unit.



[NIEHS recruiting volunteers for new study on black cohosh](#)

Women in the Triangle area of North Carolina who take black cohosh can take part in an important study on its health effects.

Science Notebook



[Variety of rodent models explored in NIEHS symposium](#)

Scientists from around the country focused on how traditional and newer strains of laboratory mice can accurately model human disease.



[Rodbell lecture features systems medicine pioneer Leroy Hood](#)

Leroy Hood, M.D., Ph.D., delivered the 2015 Dr. Martin Rodbell Lecture Series seminar, focusing on his systems approach to improving wellness.



[Children's lungs grew stronger as air pollution declined in Southern California](#)

Researchers at USC report in the New England Journal of Medicine the clear benefits to children's lung health from 20 years of improving air quality.

NIEHS Spotlight

International Symposium on Alternatives Assessment

[Symposium strengthens efforts to ensure replacement chemicals are safer](#)

The March 5-6 International Symposium on Alternatives Assessment helped advance the field of alternatives assessment.



[Solving NAE Grand Challenges — NIEHS mentors go back to school](#)

NIEHS volunteers mentor Athens Drive High School seniors as they work on National Academy of Engineering Grand Challenges.



[New method will reduce animal use in pertussis vaccine testing](#)

Workshop participants agreed on a new test method that reduces animal use in pertussis vaccine testing and proposed a plan for international adoption.



[Farris completes Society for Neuroscience Early Career Policy Fellowship](#)

Shannon Farris, Ph.D., is the first NIEHS trainee to be selected for a fellowship that trains scientists to advocate for science policy.



[NIEHS and UNC Greensboro foster environmental health research](#)

Faculty and staff from UNCG visited the institute as part of an exchange that will foster environmental health research at the university.

Science Notebook



[Adelman makes key advance in understanding cell response to environmental cues](#)

NIEHS researcher Karen Adelman, Ph.D., and colleagues found a novel interplay between embryonic stem cell signaling and transcription.



[Researchers tally substantial economic impact of EDC exposures](#)

Four papers published March 5 show substantial economic impact from exposures to endocrine disrupting chemicals in the European Union.



[Pregnancy hormone plays a role in fetal response to hormone disruptors](#)

Research by NIH New Investigator Jennifer Adibi, Ph.D., links phthalates with disrupted hCG levels in pregnant women and developmental effects in baby boys.



[NTP hosts regional meeting to highlight juvenile toxicology](#)

The Society of Toxicologic Pathology brought speakers from academia, research organizations, and government to share expertise in juvenile toxicology.



[Wetterhahn winner uses native plants to stabilize arsenic in mine waste](#)

Wetterhahn Award winner Corin Hammond studies the use of native plants as a means to stabilize arsenic in mine waste in Arizona.

Inside the Institute



[NTP trainees get practical support before SOT](#)

NTP scientists helped prepare trainees for the Society of Toxicology conference with speed interviewing and poster sessions.

Science Notebook



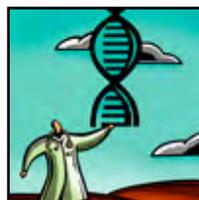
[NIEHS scientists stand out at TCRB meeting](#) 🏆

Scientists and trainees from NIEHS took full advantage of the Triangle Consortium for Reproductive Biology meeting March 14 at NIEHS.



[This month in EHP](#)

The April issue looks into the effects of climate change on a strain of pathogenic bacteria, and international policy initiatives to curb marine plastic pollution.



[GEMS spring meeting to feature NIEHS scientists and grantees](#)

The April 27 meeting will explore “Understanding How Genetic Variation Modifies Responses to Environmental Exposures.”

Extramural Research

[Extramural papers of the month](#)

- Roadmap epigenomics program maps more than 100 types of cells and tissues
- Pesticide exposure linked with ADHD behaviors in mice and people
- Mercury may be linked with autoimmune disorders
- Parental smoking during pregnancy linked with later diabetes in children

Intramural Research

[Intramural papers of the month](#)

- NIEHS researchers introduce sensitive tool to track replication enzymology
- A Notch or two in ozone susceptibility
- Plasma antioxidants are not feasible biomarkers of endotoxin-induced oxidative damage
- Poly beta and FEN1 perform a complementation role in APTX-deficient cells

Calendar of Upcoming Events

- **Apr 02**, ([webinar](#)), 1:00 – 3:00 p.m. — U.S. Small Business Funding Opportunities for Environmental Technologies at the NIEHS Superfund Research Program, U.S. Environmental Protection Agency, and National Science Foundation, [register](#)
- **Apr 03 (Off-site event)**, 8:30 a.m. – 4:30 p.m., in the great hall at the Mary Duke Biddle Trent Semans Center for Health Education at Duke University — Integrated Toxicology and Environmental Health Program spring symposium, The Cancer Exposome: Innovation at the Intersection of Environmental Exposure and Disease Pathways, [register](#)
- **Apr 06**, ([webcast](#)), 2:00 – 3:00 p.m. — 2015 National Institute for Mental Health Autism Awareness Month Special Lecture, with Thomas Insel, M.D.
- **Apr 08–09 (Off-site event)**, 9:00 a.m. – 5:00 p.m., at the William and Ida Friday Center for Continuing Education in Chapel Hill, N.C. — 39th Annual University of North Carolina at Chapel Hill Lineberger Scientific [Symposium](#), Personalized Medicine, the Cancer Genome Atlas, and the Future of Cancer Care, [register](#)
- **Apr 11 (Off-site event)**, 9:00 a.m. – 5:00 p.m., in the Miller-Morgan Health Sciences Building at North Carolina Central University (NCCU) — [Women's Health Awareness Day 2015](#), sponsored by Durham Alumnae Chapter of Delta Sigma Theta Sorority, NCCU Department of Public Health Education, and NIEHS, [register](#)
- **Apr 13–16 (Off-site event)**, at the Marriott University Park in Tucson, Arizona — [2015 joint meeting](#) of NIEHS core center directors and training grant directors, hosted by the University of Arizona College of Pharmacy
- **Apr 14**, 11:00 a.m.– noon, in Rodbell Auditorium — Distinguished Lecture by Scott Small, M.D., speaking on “Isolating Pathogenic Mechanisms Embedded Within the Hippocampal Circuit Through Regional Vulnerability”
- **Apr 14 (Off-site event)**, 4:00 – 5:00 p.m., in Toxicology Building Room 2014, Centennial Campus, North Carolina State University — Kymberly Gowdy, Ph.D., presenting “Clean up and Clear Out: A Novel Role for Scavenger Receptor BI in Environmental Lung Disease”
- **Apr 22**, 9:30 – 11:30 a.m., in Rodbell Auditorium — Administrative Professionals Day Celebration, with Earl Suttle, Ph.D., of Leadership Success International LLC, speaking on “Increasing Your Professional and Personal Power for Better Success”
- **Apr 24 (Off-site event)**, 7:45 a.m. – 5:00 p.m., at the U.S. Environmental Protection Agency (EPA) in Research Triangle Park, N.C. — [18th Annual NIEHS Biomedical Career Symposium](#), [registration](#)
- **Apr 27**, 8:30 a.m. – 3:30 p.m., at EPA — Spring [meeting](#) of the Genetic and Environmental Mutagenesis Society, [register](#) by April 20
- View More Events: [NIEHS Public Calendar](#)

IOM workshop examines role of environmental exposures in obesity epidemic

By Kelly Lenox

While exercising and healthy eating play crucial roles in the fight against obesity, current research is reshaping our understanding of the complex roots of this worrisome epidemic. The Institute of Medicine (IOM) Roundtable on Environmental Health Sciences, Research, and Medicine invited an international group of researchers to NIEHS March 2-3 to share their findings at “The Interplay Between Environmental Exposures and Obesity” workshop.

During his opening remarks, Frank Loy, chair of the [IOM roundtable](#), noted that the research community focused on the issue reflects the multifaceted origins of obesity. “It involves an interplay between the public health community and those involved in environmental health,” he said.

Interaction of complex factors

Linda Birnbaum, Ph.D., director of NIEHS and the National Toxicology Program (NTP), elaborated on the workshop’s goals. “We want to try to tease apart that interaction [between genetic factors and environmental exposures], and to reinforce the concept that obesity, with its attendant comorbidities such as diabetes and metabolic syndrome, is a multifactorial outcome,” she said.

After emphasizing the overriding importance of nutrition and physical activity, Birnbaum posed the question presenters would shed light upon during the next two days. “We have to ask whether environmental chemicals are making it harder for us all to control our weight,” she said.

Broad scope and intriguing detail

Nearly 600 people registered for the webcast and about 120 attended in person, to hear researchers from academia, government, public health, and industry discuss the issue.

A theme Birnbaum expressed in her introduction was echoed throughout the presentations. “People and the problem continue to grow larger, and there



“Only when we understand the complex origins of the likelihood of becoming obese will we be able to deal with this huge health and economic problem in our society,” Loy said, opening the workshop. (Photo courtesy of Steve McCaw)



“This problem is not restricted to the U.S. or technologically advanced countries, but is increasing in less developed countries as well,” said Birnbaum, in her welcoming remarks. (Photo courtesy of Steve McCaw)

is no single answer,” she said. Scientists shared work ranging from multigenerational studies of the effects of specific chemicals, to large-scale epidemiologic research and economic analyses (see [text box](#)).

For example, [Kristina Rother, M.D.](#), of the National Institute of Diabetes and Digestive and Kidney Diseases, discussed studies showing noncaloric sweeteners appear to increase insulin secretion and development of fat cells, and decrease the sense of reward. “There is no convincing evidence that artificial sweeteners prevent or alleviate obesity,” she said.

Obesity Society President [Nikhil Dhurandhar, Ph.D.](#), of Texas Tech University, shared research linking the adenovirus Ad36 with a greater potential for preadipose tissue to change into adipose tissue, or fat. One of several presenters participating by phone due to weather-related flight cancellations, he showed an intriguing series of maps in which the pattern of obesity increase in the U.S. resembled the spread of influenza, an infectious agent, more than it did the spread of asthma, a noninfectious disease.

Evidence linking perinatal bisphenol A (BPA) exposure in mice to increases in inflammation and systemic insulin resistance was shared by [Beverly Rubin, Ph.D.](#), of Tufts University. “It is very clear [from these and other studies] that the low doses of bisphenol A are the effective ones, and once you get across a certain border there is no effect,” she said, responding to a question about larger doses. “This may explain the controversy in the literature,” Rubin observed.

Lively discussions

Each session included ample discussion time, during which audience members and online participants raised a wide range of issues, such as neurological factors that affect appetite and activity, changes in the composition of meat and produce over the past 50 years, and decreases in sleep duration.

Many speakers echoed a familiar refrain — the traditional focus on energy balance, or comparing calories consumed against energy burned, explains only part of the obesity epidemic.

Moving forward

The workshop concluded with far-reaching discussions of research needs and policy solutions. In closing, Loy praised the character and quality of the conversation throughout the workshop, reiterating that the event was meant to share information rather than reach a consensus.

Presenters’ slides and a video recording from the workshop are available on the [IOM website](#). A workshop summary will be published later in 2015.



“The time may have come for The National Academies to do a consensus study on the issue of obesogens,” said Lynn Goldman, M.D., vice-chair of the roundtable and dean of the Milken Institute School of Public Health at George Washington University. (Photo courtesy of Steve McCaw)



Roundtable member Faiyaz Bhojani, M.D., Dr.P.H., with Royal Dutch Shell, moderated the final session on policy solutions. (Photo courtesy of Steve McCaw)

Workshop sessions

1. Framing the problem — Public and environmental health overviews highlighted the multiple pathways involved in the risk of obesity.

2. Life span view — Focusing on chemical exposures from pregnancy through adulthood, speakers addressed effects of prenatal and early life exposures to endocrine disrupting chemicals, as well as links between exposures, the onset of puberty, and obesity.

3. Biologic pathways — Scientists presented approaches to uncovering how environmental chemicals may disturb biologic pathways, including high throughput screening, studies of adipose tissue function and inflammation, and effects of environmental chemicals on energy metabolism and insulin secretion.

4. Nutrients, food additives, and antibiotics — Researchers shared their latest findings on the role of infectious agents, antibiotics, and food ingredients in the development of obesity.

5. Research needs and policy solutions — Presenters and the audience engaged in open discussion of new research directions and policies that might reduce exposure to chemicals associated with obesity.



Barbara Corkey, Ph.D., of the Boston University School of Medicine, standing at microphone, explained her team's focus while giving her presentation earlier in the day. "We began to ask whether hyperinsulinemia might be the problem rather than insulin resistance — in other words, a defect at the level of the beta cell," she said. "If that's the case, are there changes in our environment that affect basal insulin secretion?" (Photo courtesy of Steve McCaw)



Janet Hall, M.D., with the NIEHS Clinical Research Program, emphasized the role of scientists in communicating findings. "One of the important things that has come from this group of people being together today, and the weight of evidence that you reviewed, is that artificial sweeteners, for instance, are not necessarily safe," she said. "It's a very important thing that the public at large is not aware of." (Photo courtesy of Steve McCaw)



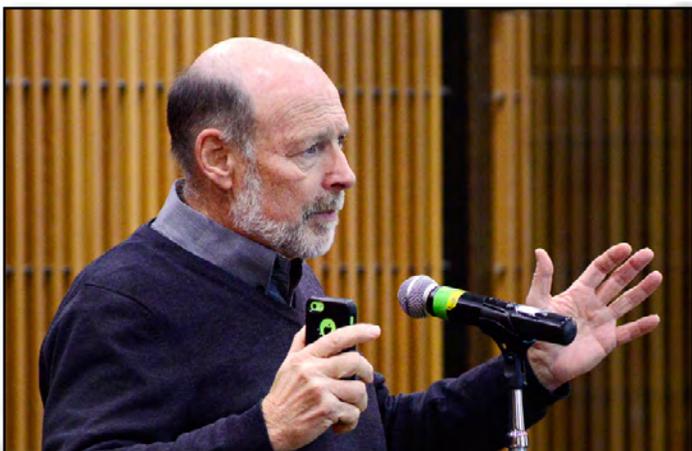
John Rogers, Ph.D., with the U.S. Environmental Protection Agency, suggested that low levels of an agent could stimulate obesity, but increasing doses could lead to other toxic mechanisms, which might in turn drive weight down. "It's not a straight line dose response, but it's increasing toxicity," he said. (Photo courtesy of Steve McCaw)



Jerry Heindel, Ph.D., with the NIEHS Division of Extramural Research and Training, oversees grants on obesity, endocrine disruptors, developmental basis of diseases, and reproductive toxicology. (Photo courtesy of Steve McCaw)



Scott Auerbach, Ph.D., with NTP Biomolecular Screening Branch, commented on research needs. “We talk about the unknowns, we talk about uncertainty, but being able to contextualize attributable risk to consumers is really critical,” he said. Auerbach’s presentation earlier had focused on using high throughput screening to identify environmental chemicals to test for obesity and diabetes outcomes. (Photo courtesy of Steve McCaw)



Jack Spengler, Ph.D., of Harvard University, issued a call for researchers to get involved in the Nurses’ Health Study III, a new cohort that includes men. Built around mobile devices, it provides new opportunities for exposure assessment. “We already have 60,000 to 70,000 recruited,” he said. (Photo courtesy of Steve McCaw)

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Council meeting delayed by snow is productive

By Ernie Hood

An East Coast snowstorm on Feb. 18 shut down the NIEHS campus, delaying the first day of the 144th [National Advisory Environmental Health Sciences Council meeting](#). The open session was held instead on March 16, as the first-ever virtual meeting of the council. Fourteen members and three ex officio members participated remotely, and NIEHS personnel met in Rodbell Auditorium. The lack of physical presence did not prevent the group from accomplishing a great deal during the proceedings, as they provided feedback and voted on several measures.

Budget stabilizes

NIEHS and National Toxicology Program (NTP) Director Linda Birnbaum, Ph.D., relayed good news on the budget — NIEHS received a funding appropriation from Congress this year, as opposed to the continuing resolutions of the past several years. “That meant a 0.2 percent increase in our health budget, and a flat budget for Superfund,” she said. “We are still not back where we were before sequestration, but we’re better than we were in 2013 or 2014.”

Birnbaum also reported news of two rounds of unexpected funds. First, the Centers for Disease Control and Prevention is transferring \$10 million to boost Ebola worker safety training over 5 years, through the NIEHS Superfund Worker Training Program (WTP). The initiative recognizes the need to provide training to many types of workers. “It’s not just medical personnel who need to be trained,” Birnbaum said. “It may be the ambulance driver, the people who clean the residence where someone with Ebola lived, and the janitors, housekeepers, and so on in hospitals. It’s a very different kind of training.”

Later in the meeting, the council approved a concept presented by WTP for Ebola biosafety training, which will include a Funding Opportunity Announcement (FOA) for extensive training to reach additional target populations. Council member Lisa Conti, D.V.M., of the Florida Department of Agriculture and Consumer Services, responded, “This is definitely something that is needed and that I wholeheartedly support.”

Focus on children’s health

The second unanticipated budget add-on comes from funds reallocated following cancellation of the National Children’s Study (NCS). The NIEHS portion totals \$57 million in fiscal year 2015. “With the redirection of the funds, there was really an emphasis on continuing to be true to the goals of the NCS,” said Gwen Collman, Ph.D., director of the NIEHS Division of Extramural Research and Training (DERT). “And one of the main thrusts of the NCS was to understand the influences of many environmental exposures on children’s growth and development.”

Of the \$57 million, \$4 million will go to the NTP **Tox21** initiative to fund studies in developmental toxicity, \$5 million will provide supplemental support for existing children’s environmental health cohorts, and the remaining \$48 million will fund an ambitious new initiative called the **Children’s Health Exposure Analysis Resource** (CHEAR).

CHEAR (see [text box](#)) will have three major components — a network of national exposure assessment laboratories, a data repository analysis and science center, and a coordinating center. Collman praised the leadership and hard work of the team of 15 administrators, led by David Balshaw, Ph.D., chief of the NIEHS



Birnbaum briefed members on legislative activities, science advances, and awards and recognitions won by NIEHS and NTP personnel. (Photo courtesy of Steve McCaw)



Collman was clearly pleased by the CHEAR funding. “The timing of this could not be better, because not only are we able to enhance our children’s environmental health program, we’re also able to launch our first initiative related to the exposome,” she said. (Photo courtesy of Steve McCaw)

Exposure, Response, and Technology Branch, and Claudia Thompson, Ph.D., chief of the NIEHS Population Health Branch, who put together the three FOAs in record time. “In my 25 years in this division, I’ve never seen a funding announcement move so quickly,” said Collman. “It’s incredible how fast you can work when you’re given something so special to work on.”

Thumbs up

The panel also approved a cookstoves concept clearance to assess interventions in low-income and middle-income countries to reduce household air pollutants, tobacco, and lung exposure. New environmental health and safety research funding opportunities in nanotechnology were also given a green light by the council.

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

CHEAR goals

- Advance understanding of the impact of environmental exposures on children’s health and development.
- Provide infrastructure for adding or expanding exposure analysis to studies involving research in children’s health.
- Measure exposures encompassing the breadth of the exposome, which is the totality of biological, psychosocial, chemical, and physical exposures.



Birnbaum and Collman welcomed George Tucker, the new head of the DERT grants management branch. Tucker came to NIEHS from the National Center for Complementary and Integrated Health, where he had served as chief grants management officer since 2004. (Photo courtesy of Steve McCaw)



Alicia Lawson, right, of the Hazardous Substance Research Branch, is another of the new NIEHS staff welcomed by Birnbaum at the council meeting. She and Heather Henry, Ph.D., left, both work with the Superfund Research Program. (Photo courtesy of Steve McCaw)



Chip Hughes, who directs WTP, spoke to the council on new Ebola worker training initiative. “This comes out of our work of many years on bioagents and infection control,” he said. (Photo courtesy of Steve McCaw)



Sharon Beard of WTP provided details of the proposed Ebola training concept, explaining that WTP has worked with grantees to restructure existing training to incorporate needs related to Ebola. (Photo courtesy of Steve McCaw)

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David Balshaw, Ph.D., left, and Alfonso Latoni, Ph.D., head of the Scientific Review Branch, listened intently to a presentation at the virtual council meeting. (Photo courtesy of Steve McCaw)



Sri Nadadur, Ph.D., who oversees the NIEHS grant program in nanotechnology, briefed the council on the nanotechnology concept, which the council voted to support. (Photo courtesy of Steve McCaw)



Claudia Thompson, Ph.D., right, briefed the council on the cookstoves concept. Cindy Lawler, Ph.D., grants program manager; William Suk, Ph.D., director of the Superfund Research Program; and Hughes were among the NIEHS staff who sat at the table normally occupied by members of the council. Things should be back to normal for the next meeting June 2-3. (Photo courtesy of Steve McCaw)

NIEHS joins meeting of Prince Charles' foundation on health care and climate change

By Audrey Pinto

NIEHS Senior Advisor for Public Health [John Balbus, M.D.](#), represented the U.S. government and the Department of Health and Human Services at a Feb. 25 meeting convened by the [International Sustainability Unit \(ISU\)](#), which is part of the Prince of Wales's Charitable Foundation. The event brought international leaders, including Prince Charles, together with experts to discuss the serious health impacts of climate change and the importance of mitigation and adaptation to reduce adverse effects.

The meeting was held in advance of the United Nations Framework Convention on Climate Change, planned for December 2015 in Paris. Ministers of Health from Barbados and the United Kingdom, as well as international

health experts from private, government, and nongovernmental organizations discussed the role of the health community in the dialogue on greenhouse gas reductions.



His Royal Highness Prince Charles, left, and Balbus conferred after the meeting, which included about 40 participants from the U.K., France, China, Barbados, and the U.S. (Photo courtesy of Paul Burns Photography)

Climate change poses grave health threat

Recognizing the importance of placing health at the center of the climate change debate, ISU framed the meeting around the messages that climate change poses significant risks to public health and well being, and that mitigation provides a significant opportunity to reduce these risks.

“Over the past few years, the World Health Organization and public health scientists around the world have identified and described the deleterious health effects of climate change,” said Balbus. “Health professionals are increasingly recognizing that substantial benefits for public health can result from actions to mitigate climate change, even as they articulate the need to strengthen the resilience of the health care sector to reduce risk.”

Messaging and communication

According to Balbus, attendees highlighted the importance of developing key messages and communication strategies to deliver credible scientific information on climate change and health to different audiences, from policymakers to the general public.

Noting the close connections between urban community resilience and public health, the participants recommended outreach to existing programs on urban resilience. The climate change adaptation and mitigation activities of these programs could help reduce environmental contributions to noncommunicable diseases, in addition to other health impacts. Participants also highlighted the need for the health sector to address its own greenhouse gas emissions through a suite of sustainability measures.

“The U.K. is providing inspiration with their many examples of integrating climate change considerations into the mainstream of public health and medical practice,” Balbus said. “This meeting helped identify a set of positive actions that the health community can take to make the difference that the world so needs, as the Prince of Wales called on us to do.”

The Prince of Wales established ISU in 2010 to build a consensus on how to resolve key environmental challenges facing the global community. The event was co-hosted by the World Health Organization.

(Audrey Pinto, Ph.D., is a technical editor for the journal *Environmental Health Perspectives*.)

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Toxicology and public health merge at SOT conference in San Diego

By Robin Mackar

Visionary biologist J. Craig Venter, Ph.D., presented the opening lecture at the annual Society of Toxicology meeting, setting the stage for an outstanding conference by providing a forward-looking focus for the field of toxicology. NIEHS and National Toxicology Program (NTP) scientists and staff brought a public health perspective to many meeting events, through presentations, posters, countless informal talks, and meetings with prospective grantees and other scientists.

Venter’s talk, “[Life at the Speed of Light](#),” zeroed in on the process of using genotype, or genetic makeup, to predict phenotype, or observable characteristics or traits. He also highlighted new developments, from understanding the human genome to synthetic genomics, the process of creating DNA from chemicals. Venter, head of the J. Craig Venter Institute, inspired the thousands who attended the March 22-26 meeting in San Diego.



Birnbaum responded to questions from the audience during the Meet the Directors session. (Photo courtesy of Society of Toxicology and Event Photography of North America Corporation)

New vision for toxicological testing

In the spirit of moving research forward, NIEHS and NTP hosted a workshop, The U.S. Tox21 Collaboration: Advances Made and Lessons Learned. The standing-room-only session featured introductory remarks by NIEHS and NTP Director Linda Birnbaum, Ph.D., and Robert Kavlock, Ph.D., deputy assistant administrator for science in the U.S. Environmental Protection Agency (EPA) Office of Research and Development.

Before introducing the speakers, Birnbaum presented [Tox21](#) milestones, including the fact that all the data is publicly available. She also outlined some of the program’s benefits. “Tox21 is a federal multiagency collaboration that is transforming the way we approach toxicology and is contributing to improved public health,” Birnbaum said. The speakers that followed shared findings that reinforced her message.

Grants and training opportunities

In addition to presenting new findings through hundreds of posters and sessions, NIEHS staff, especially those from the Division of Extramural Research and Training (DERT), spent time talking to prospective grantees and others about [grant and training opportunities](#). DERT staffed a Research Funding Information Room for two full days, giving attendees an opportunity to network and learn more about available opportunities. Another event, the Research Funding Luncheon: Multiple Perspectives on the Grant Process, held Monday, March 23, also provided time for new investigators to meet program staff and learn about the NIH grants process.

Three new funding opportunity announcements, collectively called the [Children's Health Exposure Analysis Resource](#) (CHEAR), were the subject of a webinar that NIEHS hosted during the conference. CHEAR will provide researchers access to laboratory and statistical analyses services, so they can add new children's health environmental exposure studies to current research, or expand studies already underway. Applications for the three CHEAR announcements are due April 30, 2015.

Meet the directors

SOT Vice President Peter Goering, Ph.D., served as master of ceremonies during the Meet the Directors session on Monday afternoon. Through informal dialogue with Birnbaum and Jim Jones, assistant administrator of the EPA Office of Chemical Safety and Pollution Prevention, the directors were able to discuss the missions of their agencies, highlight new directions, and respond to questions from the audience.

Birnbaum highlighted the CHEAR program and encouraged qualified participants to apply and to spread the word. She also encouraged people to share the news about the search for a new [editor in chief](#) of the NIEHS-supported journal [Environmental Health Perspectives](#).

One of the questions asked of Birnbaum was whether or too many Ph.D.'s are now being trained. She responded that it isn't a question of training too many, but that the training needs to be done differently, emphasizing that those seeking higher degrees need to be cross-trained, giving them broader perspectives and opportunities to meet workforce demands.

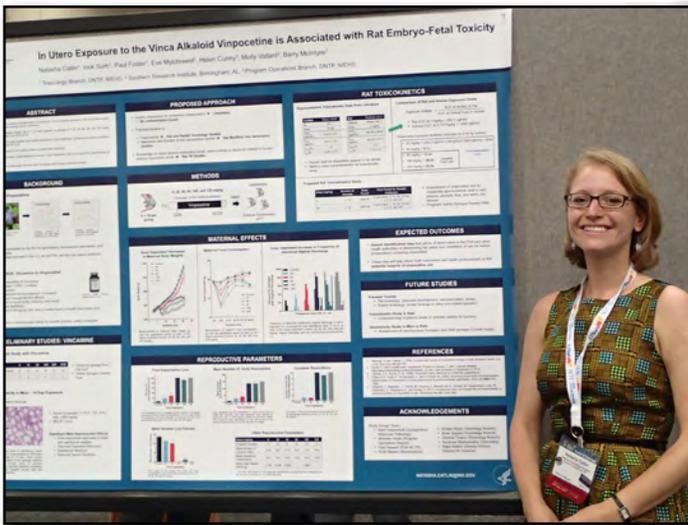
(Robin Mackar is the news director in the NIEHS Office of Communications and Public Liaison, and a frequent contributor to the Environmental Factor.)



NTP postdoctoral fellow Erin Quist, D.V.M., at computer monitor, gave hands-on tutorials on the NTP Atlas. Quist received the Roger O. McClellan Student Award at the meeting. (Photo courtesy of Robin Mackar)



Elaine Faustman, Ph.D., University of Washington toxicologist who has served on various NIEHS and NTP advisory boards, chatted with Fred Tyson, Ph.D., DERT health scientist administrator. (Photo courtesy of Lori White)



Postdoctoral fellow Natasha Catlin, Ph.D., of the NTP Toxicology Branch, was one of many NTP and NIEHS staff who presented and discussed posters. (Photo Courtesy of Lori White)



Hugh Tilson, Ph.D., left, former EHP editor in chief, and Rick Woychik, Ph.D., right, NIEHS deputy director, catch up with Sally Darney, Ph.D., of EPA. Woychik and Tilson spoke to many people about the open EHP editor-in-chief position. (Photo courtesy of Lori White)



When Yun Xie, Ph.D., left, of NTP, Chad Blystone, Ph.D., center, of NTP, and Tammy Collins, Ph.D., head of the NIEHS Office of Fellows' Career Development, were not presenting posters or leading sessions, they were available at the NIEHS exhibit, giving advice to postdoctoral researchers or answering questions about ongoing research efforts. (Photo courtesy of Robin Mackar)



Whether in the funding room, hallway, or exhibit hall, Mike Humble, Ph.D., left, of DERT, always took time to talk to students and potential grantees. (Photo courtesy of Robin Mackar)

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Valantine delivers inspiring 2015 Spirit Lecture

By Simone Otto

On March 10, NIEHS welcomed Hannah Valantine, M.D., the first National Institutes of Health (NIH) Chief Officer for Scientific Workforce Diversity, to receive the 2015 Spirit Lecture Series Award. The NIEHS Diversity Council began the lecture series in 2002, to honor Women's History Month by recognizing a notable woman who has made substantial contributions to society. Valantine expertly fulfilled the goals of the series, describing her career path and scientific achievements as well as her aims for diversifying the NIH workforce.

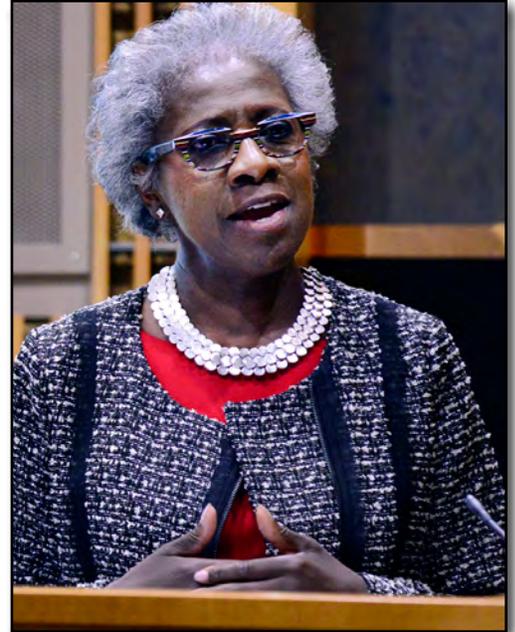
NIEHS and National Toxicology Program (NTP) Director Linda Birnbaum, Ph.D., introduced Valantine saying, "She is nationally recognized for her transformative approaches to diversity and is a recipient of the [NIH Pathfinder Award](#). In addition ... she maintained an active clinical research program that continues to yield high impact transformations in patient care."

Challenging status quo

Valantine's lecture, "Scientific Workforce Diversity: Why should a transplant cardiologist care? A career dedicated to bursting myths," began with the familiar problem of balancing professional and personal life. "I like to think about this as how we ... integrate our work and our lives, rather than feeling totally on the edge most of the time," she said.

Originally from the The Gambia in West Africa, Valantine moved to London at age 13. She studied at London University before entering a premier cardiology training program. In describing how she negotiated medical school at a time when there were only two other female cardiologists, Valantine shared three pieces of advice — seize the opportunity, understand the culture, and follow your passion.

"I saw my career really as ... dedicated to challenging the status quo," said Valantine. Sponsorship was another important aspect of her career development, which she explained meant more than mentoring. "It's an advocacy that pushes you, that does not allow you to question whether or not you can do something, because there is this implicit press from this person who is mentoring you, that you can and you must ... step forward," she said.



Valantine addressed the need to change the notion of the ideal worker. "Most of our culture was designed ... when the ideal worker was in fact the man going out to work, and the woman stayed home," she said. "Things have changed dramatically, but unfortunately our work cultures have not." (Photo courtesy of Steve McCaw)



From left, Valantine, Birnbaum, and Diane Spencer, from NTP, watched "Women in History," the inspiring film by Brad Collins, NIEHS Diversity Council chair, which traditionally opens the Spirit Lecture. (Photo courtesy of Steve McCaw)

Linked video: (Launches in new window)

Watch Valantine and others discuss mentorship in this video by the Women of Color Research Network, sponsored by the National Institute of Biomedical Imaging and Bioengineering. (4:14)

Download Media Player: Flash [↗](#)



Valantine explained to a rapt audience why the so-called pipeline problem is really a funnel problem. The issue is not getting people from underrepresented groups interested in sciences, she said, but retaining them. (Photo courtesy of Steve McCaw)

Unwavering commitment

Around 1982, Valantine was warned against her chosen path, when a superior commented, “Oh, so you want to be a cardiologist — a woman and black?” She was undeterred and followed her passion for cardiology to Stanford University, to study with the late Norman Shumway, M.D., Ph.D., who is often referred to as the father of heart transplantation.

Working at the forefront of new technologies in heart transplantation and identification of transplant risk factors, Valantine collaborated with bioengineer Stephen Quake, D.Phil. They developed and validated a blood test for donor DNA that can be used to noninvasively diagnose rejection in the early stages.

Scientific workforce diversity

According to Valantine, unconscious bias is a major factor in slowing change, as it affects our perception of what a scientist is, in terms of gender and race. She described a Stanford study that used talk as an intervention and succeeded in reducing this bias. As a scientist and chief officer for scientific workforce diversity at NIH, Valantine has a refreshing solution-based approach to diversity and plans to bring scientific rigor to the process.

Former speakers in the Spirit Lecture Series include Rita Colwell, Ph.D., the first woman to head the National Science Foundation, Nancy Andrews, M.D., Ph.D., the first female dean of Duke University School of Medicine, and Carol Folt, Ph.D., the first female chancellor of University of North Carolina at Chapel Hill.

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



The event ended with the presentation of the 2015 Spirit Lecture Series poster by members of the NIEHS Diversity Council. From left, Angela King-Herbert, D.V.M.; Molly Vallant; Spencer; Valantine; Veronica Robinson; and Collins (Photo courtesy of Steve McCaw)

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Symposium strengthens efforts to ensure replacement chemicals are safer

By Ernie Hood

The field of alternatives assessment, which is the effort to identify and use safer alternatives to chemicals, took a major step forward March 5-6 at the [International Symposium on Alternatives Assessment](#), held at the National Institutes of Health (NIH) campus, Bethesda, Maryland. The symposium provided a collegial forum for government staff, university researchers, industry sustainability professionals, advocates, and other stakeholders to address this emerging field.

Despite a major snowstorm, which played havoc with attendance and caused the first day's events to be moved to a local hotel, the attendees achieved a consensus that the field of alternatives assessment is poised for rapid advancement and increasing acceptance.

The weather prevented NIEHS and National Toxicology Program (NTP) Director Linda Birnbaum, Ph.D., from attending, but Christopher Weis, Ph.D., a Bethesda-based senior science advisor in the Office of the Director, stepped in to give the keynote address and participate in a panel discussion on related federal agency opportunities and needs.

Consider the need

The field of alternatives assessment is built on the concept that before choosing a chemical for any purpose — whether a cleaning agent, pesticide, laboratory chemical, or other compound — people should consider whether they actually need to use the chemical at all, and if so, whether there may be a safer alternative.

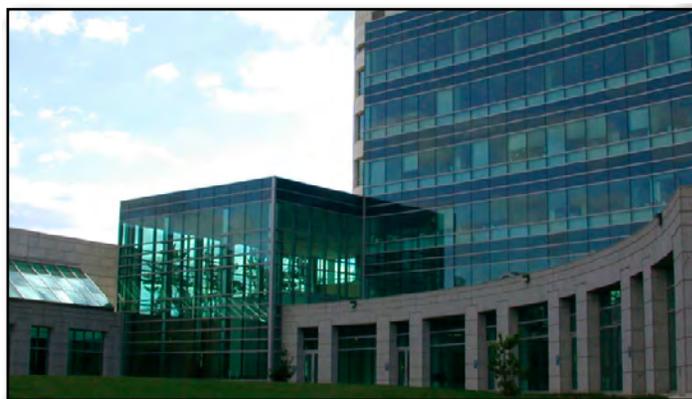
“We know that many chemicals that are in use do have safer alternatives that can be deployed to effect the same result,” said Weis. “They are safer, they are better for the environment, and they’re better for public health.”

A field on the brink

Many participants observed that, although alternatives assessment is not new, the discipline still needs to achieve more formal recognition. Organizers hoped to foster understanding of the gaps in knowledge and methods, help identify research agenda elements, and advance and support the growing field of alternatives assessment.



NIEHS participants in the symposium included, from left, Katie Pelch, Ph.D., training fellow in the NTP Office of Health Assessment and Translation; Trisha Castranio, sustainability analyst in the Health and Safety Branch; Bennett; and Weis. (Photo courtesy of April Bennett)



The NIH Natcher Conference Center was blanketed by snow on the first day of the symposium, but hosted the second day as scheduled. Attendees achieved a consensus that the field of alternatives assessment, which Weis called “the business end of green chemistry,” is poised for rapid advancement and increasing acceptance. (Photo courtesy of NIH)

“We’ve come a long way,” said Joel Tickner, Sc.D., from the Lowell Center, in his closing remarks. “I truly feel that we have a nascent field of science policy inquiry coming.” Tickner spoke on alternatives assessment at NIEHS in February (see [story](#)).

Sally Edwards, Sc.D., from the Lowell Center suggested that to continue progress toward establishing a more formally organized community of practice, a research and practice agenda should be fleshed out and ultimately published and disseminated.

According to Weis, all of the stakeholders support the alternatives assessment concept. “It’s good for everyone,” he said. “It’s good for industry, academia is very interested in supporting the effort, and the government has a responsibility. We’re actively working to reduce the use of chemicals, and in cases where it’s appropriate, to substitute safer alternatives.”

The [Lowell Center for Sustainable Production](#) at the University of Massachusetts organized the event, ably assisted by April Bennett of the NIEHS Office of the Director. NIEHS was a cosponsor, along with the U.S. Environmental Protection Agency and ToxServices LLC, a Washington, D.C. scientific consulting firm.

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

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Chemical Commons

In Oct. 2012, a group of environmental health scientists, advocates, funders, and policymakers met for two days to discuss “Building a Chemical Commons: Data Sharing, Alternatives Assessment, and Communities of Practice.” A subcommittee followed up, refining a consensus set of principles, now known as [The Commons Principles for Alternatives Assessment](#). Excerpts are given below.

Definition

Alternatives assessment is a process for identifying, comparing, and selecting safer alternatives to chemicals of concern (including those in materials, processes, or technologies) on the basis of their hazards, performance, and economic viability. A primary goal of alternatives assessment is to reduce the risk to humans and to the environment by identifying safer choices.

Principles

- Reduce hazard
- Minimize exposure
- Use best available information
- Require disclosure and transparency
- Resolve trade-offs
- Take action

Solving NAE Grand Challenges – NIEHS mentors go back to school

By Geoffrey Feld

How does one prepare high school seniors for 21st century higher education and careers? Shane Barry, a teacher at Athens Drive High School in Raleigh, North Carolina, asked his students to tackle the [National Academy of Engineering \(NAE\) Grand Challenges](#). They’ll be getting help from NIEHS scientists and staff (see [sidebar](#)), who visited March 13 to help them get started.

The seniors in Barry’s course will apply their science, technology, engineering, and mathematics (STEM) education to real-world problems. Using engineering principles, the students will break down complex problems into discrete and testable goals. The course culminates in a capstone project — working in small groups, the students will select a Grand Challenge and develop an original solution.

“This is just one of several activities we have lined up this spring to support STEM education in regional school districts,” said Ericka Reid, Ph.D., director of the Office of Science Education and Diversity (OSD). “We’re excited by the response we’ve received.”

Local networking pays off

To facilitate Barry’s ambitious plan, Kristin Thomas, STEM coordinator at the school, attended a networking event, sponsored by [WakeEd Partnership](#), to match educators with local STEM professionals. There she met Huei-Chen Lao, OSD coordinator for K-12 science education and outreach.

Lao pitched the school’s plan at NIEHS and attracted an enthusiastic group of researchers and staff to serve as mentors for Barry’s students. The newly minted NIEHS mentors visited the school to get acquainted with the budding engineers. They found students completing designs for sustainable local public works projects and observed short presentations by professionally dressed students, who were elected by each group and referred to as smart city planners.

Equipped with the right skills

Although the NIEHS mission is directly relevant to some of the NAE challenges, such as engineering better medicines and advancing health informatics, others, including providing energy from fusion, seem better suited for physicists. Janine Santos, Ph.D., of the NIEHS Epigenetics and Stem Cell Biology Laboratory, assured students that the scientists could help. “Not because we are engineers, but because of the skill sets that we have,” she said. The engineering principles taught in Barry’s course are at the core of biological research, regardless of the technical background.

NIEHS mentors stressed the importance of effective communication for a successful collaboration. Oswaldo Lozoya, Ph.D., also of the Epigenetics and Stem Cell Biology Lab, explained that scientists become well versed in language specific to their field of study, but they could just as easily train in a different field with different language. “Invite us to get acquainted with the language you [will] be using for your projects, and then we can help you efficiently,” he said.

In the coming weeks, the groups will select their challenges and reach out to NIEHS mentors for guidance. And mentors will be invited to attend the final presentations of the solutions. Santos said the mentors view the pairings as an exchange, because students and mentors will learn from each other.

(Geoffrey Feld, Ph.D., is an Intramural Research Training Award fellow in the NIEHS Genome Stability Structural Biology Group.)



Lao coordinates activities promoting STEM education, encouraging students to seek careers in biomedicine, especially the environmental health sciences. (Photo courtesy of Steve McCaw)

NIEHS volunteers

- **Sara Andres, Ph.D.**, visiting fellow, NIEHS Genome Integrity and Structural Biology Lab (GISB)
- **Neal Englert, Ph.D.**, Intramural Research and Training Award (IRTA) fellow, GISB
- **Geoffrey Feld, Ph.D.**, IRTA fellow, GISB
- **Kenda Freeman**, research and communication specialist for NIEHS contractor MDB, Inc.
- **Oswaldo Lozoya, Ph.D.**, Fellow from Epigenetics and Stem Cell Biology Lab (ESCB)
- **Sara Mishamandani**, research and communication specialist for MDB, Inc.
- **John Roberts, Ph.D.**, staff scientist, ESCB
- **Janine Santos, Ph.D.**, staff scientist, ESCB



NIEHS scientists Englert, left, and Lozoya helped inspire students in the ambitious engineering challenges posed by NAE. (Photo courtesy of Huei-Chen Lao)



Barry, standing, addresses his students and the NIEHS mentors — Santos standing at back, and front table, clockwise from left, Roberts, Anders, Feld, and Englert. (Photo courtesy of Huei-Chen Lao)

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New method will reduce animal use in pertussis vaccine testing

By Catherine Sprankle

Participants at a March 4-5 workshop, including regulators and vaccine manufacturers, agreed on a new method that uses fewer animals for pertussis vaccine safety testing, and a plan was proposed for international adoption of the test.

Scientists with the National Toxicology Program (NTP) and international collaborators organized the workshop, which was hosted by the [National Centre for the Replacement, Refinement, and Reduction of Animals in Research](#) at its headquarters in London.

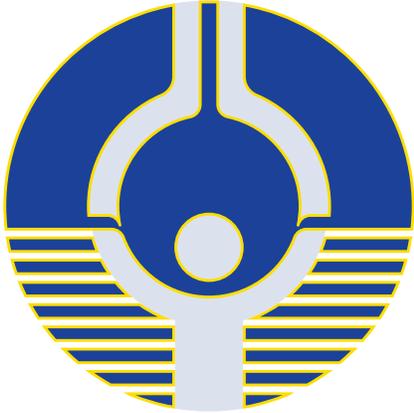
Interest in alternatives to pertussis vaccine tests

Acellular pertussis vaccines, which contain proteins purified from bacteria, rather than whole cells, were developed in the 1980s. Prior to marketing these vaccines, manufacturers must confirm the absence of residual pertussis toxin by using the rodent-reliant murine histamine sensitization test, or HIST. There is widespread interest among vaccine manufacturers and animal welfare advocates in finding a nonanimal alternative to the test, because the technically challenging test requires up to 60 animals per test, and the animals experience significant pain and distress.

Pertussis

Pertussis, also known as whooping cough, is a contagious respiratory disease that can be fatal.

Recent outbreaks of pertussis have raised awareness of the importance of vaccination, which is the most effective prevention against the disease.



The International Working Group for Alternatives to HIST, established in 2011, has addressed this issue through a series of four workshops. Participants reviewed available alternatives, recommended studies to evaluate those alternatives, and considered requirements for regulatory acceptance. Scientists with the [NTP Interagency Center for the Evaluation of Alternative Toxicological Methods \(NICEATM\)](#) have participated in the working group from the beginning.

“This ongoing effort serves as an excellent example of a successful collaboration between regulators and industry scientists,” said Dave Allen, Ph.D., who presented a summary of the previous workshops. “Working together to identify valid nonanimal alternatives for biologics testing, this group of experts is making significant progress towards reducing our reliance on animal use.” Allen is a researcher with NICEATM support contractor Integrated Laboratory Systems Inc. (ILS).

Successful workshop series

The 43 international experts who attended the March workshop examined data from a multilaboratory study. The study evaluated an assay that uses a cell line derived from Chinese hamster ovarian tissue to measure pertussis toxin in vaccine samples that contain reference preparations, or specific quantities of added toxin. The experts concluded that the assay worked adequately, and they recommended that vaccine manufacturers begin using the assay alongside current HIST testing to demonstrate its validity for their specific products.

Participants also discussed implementing an approach that would allow manufacturers to waive testing entirely under certain circumstances, and regulatory agency representatives attending the meeting agreed in principle to this suggestion.

Proceedings from the workshop will be submitted to *Pharmeuropa Bio* and *Scientific Notes* for publication later this year.

(Catherine Sprankle is a communications specialist with ILS.)

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Farris completes Society for Neuroscience Early Career Policy Fellowship

By Greg Buchold

In January, NIEHS trainee Shannon Farris, Ph.D., completed her year as a 2014 Society for Neuroscience Early Career Policy Fellow, and in February, she began a year of mentoring 2015 fellows. Farris, an Intramural Research and Training Award fellow in the NIEHS Neurobiology Laboratory, is the first NIEHS fellow to receive this opportunity.

Finding alternatives to animal testing

Federal agencies work to reduce the use of animals in research and testing. Methods that use fewer or no animals, or that reduce animal pain and distress, are referred to as [alternative methods](#).

NICEATM supports NTP high-throughput screening projects and conducts other projects relevant to alternative methods development.

The award trains early career scientists to advocate for federal, state, and local science policy that supports scientific research. Because activities largely take place in the fellow's home district, postdoctoral mentors can more easily support their trainee's policy efforts, knowing that lab work will not be put on hold.

"This fellowship gave me the opportunity to learn first hand how legislators make science policy decisions," Farris said. "It also gave me the tools and skills needed to advocate for biomedical research to our North Carolina elected officials. Most importantly, it allowed me to do so while staying at the [lab] bench. It's been a great year."

Concrete accomplishments

The fellowship primarily supports travel funding to attend the Society for Neuroscience's Capitol Hill Day, an annual event in Washington, D.C.

Fellows and senior scientists meet with Senate and House members from their states, to discuss scientific research and its effects in their congressional districts.

During Farris's year as a policy fellow, she reactivated the 160-member local chapter of the Society for Neuroscience, which hosted Congressman David Price at a science policy town hall in Sept. 2014 (see [story](#)).

Farris and the chapter, along with local universities, also got involved in public outreach events at area science museums during national Brain Awareness Week this past March. She also participated in the Rally for Medical Research Day, Sept. 17, 2014, in Washington, D.C.

The award also provides informational resources to fellows, to keep them apprised of emerging policy issues, the Congressional calendar, and dates that their local representatives are in their home districts.

Scientist, advocate, mentor

At NIEHS, Farris is an Intramural Research and Training Award fellow in the Synaptic and Developmental Plasticity Group, headed by Serena Dudek, Ph.D. Farris studies the function of the CA2 region of the hippocampus, in the brain. In particular, she is working to determine the molecular mechanisms underlying unique forms of plasticity in the CA2 region and its susceptibility to disease, such as schizophrenia. "Farris has a quick understanding of the way parts fit into the whole," Dudek said. "That gives her valuable insight both in the lab and in her work locally to promote research and related activities."

As the first NIEHS fellow selected for the award, Farris took care to comply with federal ethics laws, which prohibit certain political activities by federal employees. "My involvement was cleared by the NIEHS ethics office, and I carried out my activities as a private citizen on my own time, rather than a representative of NIEHS," Farris said.

In addition to continuing her research, Farris plans to mentor incoming 2015 Early Career Policy Fellows and to continue to seek opportunities to promote science policy as a postdoctoral fellow.



Farris posed with others on Hill Day in 2014. From left, Allen Segal, J.D., with the Society for Neuroscience; Farris; North Carolina Senator Kay Hagan; Peter Kalivas, Ph.D., professor of neuroscience at the Medical University of South Carolina; and Mark Rasenick, Ph.D., distinguished professor at the University of Illinois at Chicago College of Medicine. (Photo courtesy of the office of former Senator Kay Hagan)



At the Rally for Medical Research, Farris, back row, third from right, joined about 300 people from 30 states, including scientists, nonprofit organizations, and patients, to promote continued investment in medical research. (Photo courtesy of the American Association for Cancer Research)

(Greg Buchold, Ph.D., is a former NIEHS postdoctoral fellow in the Reproductive and Developmental Biology Laboratory.)

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NIEHS and UNC Greensboro foster environmental health research

By Joe Balintfy

A group of faculty and staff from the University of North Carolina at Greensboro (UNCG) visited NIEHS March 10 as part of an exchange that will foster environmental health research at the university. The visitors learned about the institute, its opportunities, and the review process for environmental health research grants. NIEHS staff will reciprocate April 7, traveling to UNCG to talk with students about environmental health, NIEHS research, and paid internships.

John Schelp, NIEHS special assistant for community engagement and outreach, gave an overview and campus tour, and Ericka Reid, Ph.D., director of the Office of Science Education and Diversity, led a discussion on year-round and summer internships.

“I’m very glad to know that our outreach is making an impact,” said Reid. “We’re reaching out to more colleges and universities, here in this region and further afield, and they are interested in what we have to offer.”



UNCG

The first of two meetings

Much like last year's visit by University of Massachusetts faculty (see [story](#)), this meeting gave the UNCG guests practical information on working with NIEHS and the National Institutes of Health (NIH).

"I think a good collaboration and partnership will come from this," said Patrick Madsen, Ph.D., director of the career center at UNCG. "It's definitely going to help UNCG faculty connect to the grant and research potential that NIH and NIEHS have to offer."

Perspective from extramural experts

One attraction for the visiting UNCG faculty was the grants workshop, which staff from the NIEHS Division of Extramural Research and Training (DERT) condensed from a 17-hour workshop into about an hour.

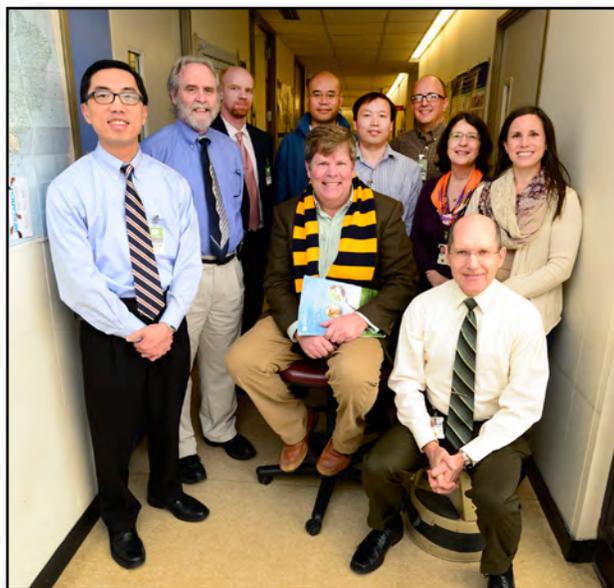
"I gave a broad overview of the NIH and NIEHS extramural worlds," said DERT Deputy Director Pat Mastin, Ph.D. "Some of these faculty may be eligible for grants, so I talked about the kinds of grants available and about the process."

Caroline Dilworth, Ph.D., Barbara Gittleman, and Mike Humble, Ph.D., all from DERT, shared more details. For example, Gittleman, a grants management specialist, explained the Academic Research Enhancement Award grant, which is designed for smaller institutions, like UNCG.

Norman Chiu, Ph.D., associate professor of chemistry at UNCG, is actively seeking NIH support and found the meeting very helpful. "It's given me a much better picture on how to prepare a better NIH proposal," he said.

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

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Standing, from left, Chiu; Mastin; Madsen; Qibin Zhang, Ph.D. (UNCG); Zhenquan Jia, Ph.D. (UNCG); Aubrey Roland Turner (UNCG); Gittleman; and Dilworth. Sitting, from left, Schelp and Humble. Turner, a grant proposal development specialist at UNCG, was an NIEHS summer intern 20 years ago. (Photo courtesy of Steve McCaw)



"As a UNCG alum, I'm honored to share what we're doing here, and how we can better connect with faculty and students," said Reid. "It's a huge part of what we're about here at NIEHS." (Photo courtesy of Steve McCaw)

Clinical Feature

New NHALES study will help asthma sufferers

By Robin Arnette

Individuals with moderate to severe asthma can receive free treatment and medications by joining a new health study at the NIEHS Clinical Research Unit. The Natural History of Asthma with Longitudinal Environmental Sampling study, or NHALES, will help scientists understand how the environment affects asthma symptoms. In particular, NIEHS scientists will examine how bacteria living in and on humans and in their homes, known collectively as the microbiome, may be associated with asthma activity.

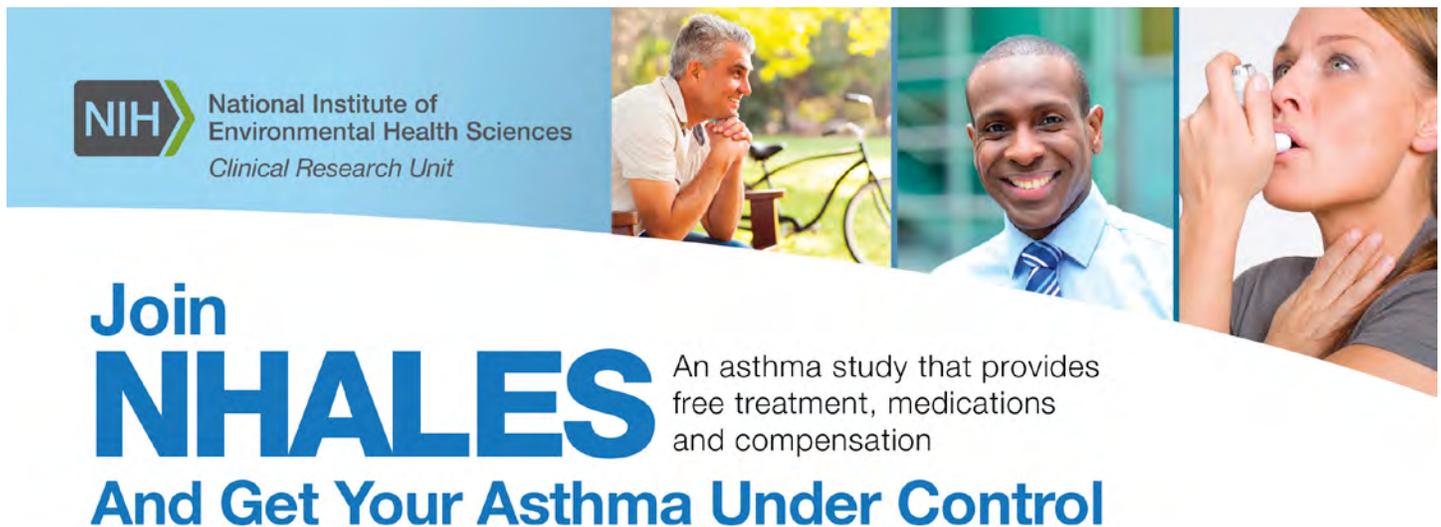
Stavros Garantziotis, M.D., lead researcher for NHALES, said volunteers will visit the Clinical Research Unit in Research Triangle Park, North Carolina, approximately twice a year during the course of the five-year study. Study members will undergo physicals and breathing tests, give biological samples, and complete questionnaires. They will be compensated financially for their time, and will receive an additional benefit. "NHALES participants will be seeing an asthma specialist twice a year, or more frequently if they experience asthma attacks, and will get their medicines at no cost," Garantziotis said.

Asthma patients who are 18-60 years old, nonsmokers, and not pregnant or breastfeeding are eligible to join NHALES.

NHALES contact: NHALES@nih.gov or 919-541-9846



Garantziotis is head of the Matrix Biology Group, which studies cell-matrix interactions in the response to lung injury from environmental sources or certain immune responses. (Photo courtesy of Steve McCaw)



The banner features the NIH logo on the left, with the text "National Institute of Environmental Health Sciences Clinical Research Unit". To the right are three images: a man sitting outdoors, a man in a blue shirt smiling, and a woman using an inhaler. Below the images, the text reads: "Join NHALES An asthma study that provides free treatment, medications and compensation And Get Your Asthma Under Control".

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NIEHS recruiting volunteers for new study on black cohosh

By Kelly Lenox

Researchers at NIEHS are recruiting women in the Raleigh-Durham-Chapel Hill area of North Carolina for a clinical study on black cohosh. Women who take the herbal supplement for hot flashes, cramps, or other symptoms can take part in this important study on the health effects of black cohosh.

“Collaborating with the NIEHS Clinical Research Unit gives us an important opportunity to follow up on findings from our NTP [National Toxicology Program] animal studies, by evaluating potential biomarkers of black cohosh use in women in real-life exposure situations,” said [Kristine Witt](#), head of the NTP Genetic Toxicology Group. “The study will compare several specific endpoints, such as folic acid and vitamin B12 levels, in two populations of women — those who have been taking black cohosh for at least 3 months, and those who have never taken black cohosh.”

To participate, a woman must be healthy, neither pregnant nor breastfeeding, over the age of 18, and already taking a black cohosh supplement. For this study, healthy means feeling well and able to perform normal activities. A woman with a chronic condition, such as high blood pressure, is considered healthy if she is being treated and the condition is under control.

Qualified participants must make a visit to the NIEHS [Clinical Research Unit](#) in Research Triangle Park to donate a blood sample. Volunteers will be compensated up to \$50.

For questions about the Black Cohosh Study, call 919-316-4976.

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Witt's group is responsible for testing chemicals of interest to NTP, to see if they trigger DNA changes that may cause adverse health effects. (Photo courtesy of Steve McCaw)

Science Notebook

Variety of rodent models explored in NIEHS symposium

By Robin Arnette and Kelly Lenox

An NIEHS symposium, Population-Based Rodent Resources for Environmental Health Sciences, featured scientists from around the country addressing ways that traditional and newer strains, or models, of laboratory mice can accurately reflect human disease. Besides traditional inbred strains, or strains that are essentially clones, researchers are using diverse, or outbred, populations, which are thought to reflect population-wide exposures in humans.

Besides presentations, panel discussions, and a poster session, planners of the March 18-19 symposium took advantage of the gathered experts and scheduled breakout sessions for the second day. “We wanted to use all the expertise to brainstorm experimental designs for these new population-based rodent resources,” said lead organizer Kim McAllister, Ph.D., health scientist administrator in the NIEHS Division of Extramural Research and Training. “That gives NTP [National Toxicology Program] and the EPA [U.S. Environmental Protection Agency] more information on the challenges and opportunities these new models provide.”

Mouse strains that model human genetic variability

David Threadgill, Ph.D., of Texas A&M University, set the stage with a discussion of [Collaborative Cross](#) (CC), a mouse strain developed to mimic the variable genetic backgrounds in the human population. When tested with Ebola, for instance, the distribution of responses in the CC mice was much closer to that seen in humans than was found in tests on traditional strains.

The growing variety of strains helped Ivan Rusyn, M.D., Ph.D., also from Texas A&M, study why a few clinical trial participants taking acetaminophen developed signs of liver injury. With one hybrid mouse and 36 inbred strains, he and his team performed genetic analysis, which told them the liver was failing due to an inflammatory response and because 26 genes were triggering the cell death process.

Mouse models may also be used to reduce the cost of developing medicines, which is increased when synthesized drugs fail during clinical trials, according to Alison Harrill, Ph.D., from the University of Arkansas for Medical Sciences. “Since these preclinical mouse models do a good job of replicating human illness, they will help us narrow the focus to making compounds that work in people,” she said.

Computational analysis

The importance of computational analysis was underlined by Daniel Pomp, Ph.D., from University of North Carolina at Chapel Hill. “No matter how good your model is, and no matter how nicely you design your experiment, what you get out is mostly dependent on the computational and statistical tools available to analyze the data.”



“Many recently published proof-of-principle studies, showing the diverse utility of these population-based rodent models in the environmental health sciences and toxicology fields, were highlighted during the meeting,” said McAllister, pointing to the Ebola and benzene studies. (Photo courtesy of Steve McCaw)

Mouse strains with diverse genetic material call for new approaches to data analysis, which can generate new insights. Eleazar Eskin, Ph.D., from the University of California, Los Angeles, and his team developed analytical methods to examine gene-environment interactions. “Our approach ... does not require prior knowledge about environmental variables to look for potential genes involved in the effects,” he explained. “This gives us a great opportunity to move forward,” Eskin said.

Applying to disease and moving forward

Several speakers addressed the study of particular diseases. Elissa Chesler, Ph.D., from the Jackson Laboratory, has used the Diversity Outbred mouse to more precisely identify the loci involved in notoriously variable behavioral traits, which have been traditionally mapped to larger regions of the genome. “We now have the level of precision we need to identify molecular networks that are associated with these behavioral traits,” she said.

After the talks, participants broke into four groups to discuss experimental designs and test cases. Reports from the breakout sessions addressed pros and cons of different models, study proposals, and how the use of diverse models affects the concept of reproducibility.

“It’s been a fabulous meeting,” said Linda Birnbaum, Ph.D., director of NIEHS and the National Toxicology Program. “The Collaborative Cross and Diversity Outbred mouse offer tremendous opportunities for screening chemicals,” she said.

A full meeting agenda, including abstracts of all talks and posters, is available on the [meeting Web page](#). Organizers will also post a summary of the symposium, once it is completed.



“When we don’t see anything in our animal models, it may not mean nothing is happening — it may mean we haven’t used a sensitive model,” said Birnbaum, summing up one of the take-away messages of the meeting. (Photo courtesy of Steve McCaw)



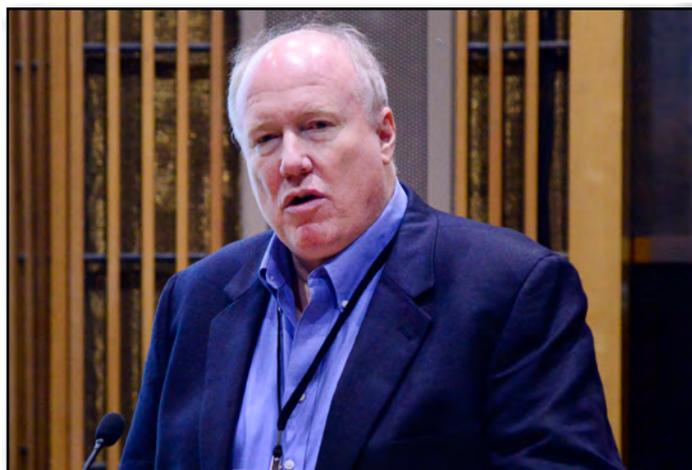
From left to right, Terrance Kavanagh, Ph.D., University of Washington; Rick Paules, Ph.D., acting chief of the NIEHS Biomolecular Screening Branch; and Nigel Walker, Ph.D., NTP deputy division director for science, were among the large audience at the symposium. (Photo courtesy of Steve McCaw)



Fred Tyson, Ph.D., NIEHS health scientist administrator, listened as Amelie Baud, Ph.D., a postdoctoral fellow at the European Bioinformatics Institute, describes her research on the effects that the genetic makeup of cage-mates has on important clinical traits. (Photo courtesy of Steve McCaw)



From right to left, Birnbaum; meeting co-organizer David Balshaw, Ph.D.; and McAllister had front row seats during the symposium. Balshaw, chief of the Exposure, Response, and Technology Branch in the NIEHS Division of Extramural Research and Training, moderated the first day's morning session. (Photo courtesy of Steve McCaw)



Speaking of the eight founding strains of the Collaborative Cross mouse, Threadgill said, "They seeded the population with a much higher level of genetic polymorphisms [variations] than we would have had if we had just used standard laboratory strains." (Photo courtesy of Steve McCaw)



Kavanaugh, left, listens as NTP toxicologist Kristine Witt, center, discusses her work with Diversity Outbred mice during her poster presentation. (Photo courtesy of Steve McCaw)



Weihshueh Chiu, Ph.D., of Texas A&M University, spoke on risk assessment, citing the power of population-based resources. "When you add population variability, the power goes beyond genes and helps identify pathways involved in susceptibility or resistance to environmental factors," he said. (Photo courtesy of Steve McCaw)



Gary Churchill, Ph.D., and others from The Jackson Laboratory, developed the Diversity Outbred mouse to test responses to benzene exposure. "Genetically diverse mice provide a reproducible response to benzene exposure variation that reflects the range of responses that can be expected in the human population," he said. (Photo courtesy of Steve McCaw)

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Rodbell lecture features systems medicine pioneer Leroy Hood

By Robin Arnette

Leroy Hood, M.D., Ph.D., has spent his entire career thinking about and creating technologies that have changed the way researchers decipher the fundamental principles of biology. His current endeavor, called P4 medicine, uses a systems approach to studying disease and its counterpart, wellness. Hood addressed the four P's of his approach to medicine — predictive, preventive, personalized, and participatory — during his 2015 Dr. Martin Rodbell Lecture Series seminar March 10.

NIEHS and National Toxicology Program (NTP) Director Linda Birnbaum, Ph.D., introduced Hood to the audience, which included Barbara Rodbell, the widow of the late Nobel Laureate Martin Rodbell, Ph.D. NTP toxicologists Warren Casey, Ph.D., and Kristine Witt, cohosted the presentation.



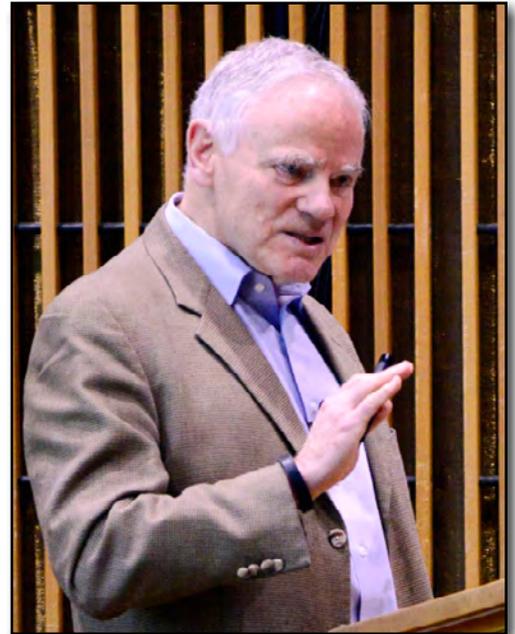
Systems medicine seeks to quantify wellness

As president and cofounder of the Institute for Systems Biology (ISB), a nonprofit biomedical research organization in Seattle, Hood thought that if he and his team could track wellness and watch its transition into disease, they could see the first mechanisms of illness. That would help them understand how to put people back onto a path to wellness.

“This wellness endeavor will create a whole new industry that will be separate from what I call the disease industry, which is the current health care industry,” Hood said. “I predict that in 10-15 years, the wellness industry will far exceed the market captured by the disease industry.”

According to Hood, there are three major principles behind this goal, which he calls P4 medicine or systems medicine. First, every individual patient's personal and health information will be used to create a data set, and then scientists will use computational tools to create a profile for each individual. Hood's team has already successfully modeled data for 100 people. His goal now is to conduct a long-term study of 100,000 people (see sidebar).

Second, using this approach, researchers can identify biological networks, which are the information channels that govern development, normal body functions, and aging. Hood said that when these channels become altered, they lead to disease.



In addition to receiving the National Medal of Science from President Obama in 2013, Hood is a member of three national academies — the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. (Photo courtesy of Steve McCaw)



“Dr. Hood is noted for his ability to fund, develop, and move into new technologies,” said Birnbaum in her introduction. “He has founded a whole list of companies, which are really pushing the boundaries of technology.” (Photo courtesy of Steve McCaw)

Third, data collection should be as global as possible, to capture the unknown elements of particular diseases. Hood said this would allow the ISB team to look at the dynamics of the system and see how they change across time and place.

Early P4 studies

Hood went on to explain some of his early P4 studies. To understand the dynamics of neurodegenerative conditions caused by prions, or misfolded proteins, Hood collaborated with George Carlson, Ph.D., of the McLaughlin Research Institute in Great Falls, Montana. The team found 300 genes potentially involved in neurodegeneration. Further analyses uncovered two major findings. First, these genes turned on four processes in sequential order — accumulation and replication of prions, activation of microglia, degeneration of synapses, and death of neuronal cells. Second, the biomarkers for these processes could be detected in the blood. A biomarker is a molecule, detected in the body, that is a sign of a particular process.

In another example, Hood explained that pulmonary oncologists see thousands of patients that have nodules in their lungs. Many patients elect to undergo surgery to remove the nodules, but 40-50 percent of the patients have benign growths.

Using the systems approach, Hood and his team identified 471 molecules relevant to lung cancer, and additional computer modeling narrowed it down to 13. These 13 proteins were then used as a biomarker panel, allowing the researchers to rule out benign nodules in patients with 90 percent accuracy. “We prevented more than a third of the unnecessary surgeries, saving the healthcare system about \$3.5 billion a year,” Hood said.

Human disease exhibits enormous biological complexity, and it seems that P4 may be another of the paradigm changes that Hood will impart to the world.



Barbara Rodbell, fourth from left, and her guests sat up front, with seminar hosts Casey and Witt behind them. Casey summed up Hood’s talk by saying, “Dr. Hood has a strong track record of conceiving and implementing approaches that have fundamentally changed the way we do science. His P4 initiative is now revolutionizing our approach to wellness and health care.” (Photo courtesy of Steve McCaw)

The 100K Wellness Project

The 100K Wellness Project will enroll 100,000 healthy individuals with the goal of transforming health care. The project began in 2014 with 100 individuals, and it will begin to scale up later in 2015.

These 100 wellness pioneers have undergone complete genome sequencing, and they submit to detailed lab tests every three months. Hood said that after compiling the initial results, he quickly saw people separating into groups. Some remained well and extended their health, while others transitioned into disease.

“If we think of each person as having a wellness well, most of us would be near the bottom of our well,” he added. “By looking at your data plot, we can get actionable possibilities that will elevate you up toward your potential wellness.”



Hood, left, and Barbara Rodbell pose with the Rodbell Lecture sculpture — a bronze casting that NIEHS presents to speakers of this illustrious seminar series. Rodbell has attended every Rodbell lecture since her husband gave the first talk of the series in 1998. (Photo courtesy of Steve McCaw)

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Children's lungs grew stronger as air pollution declined in Southern California

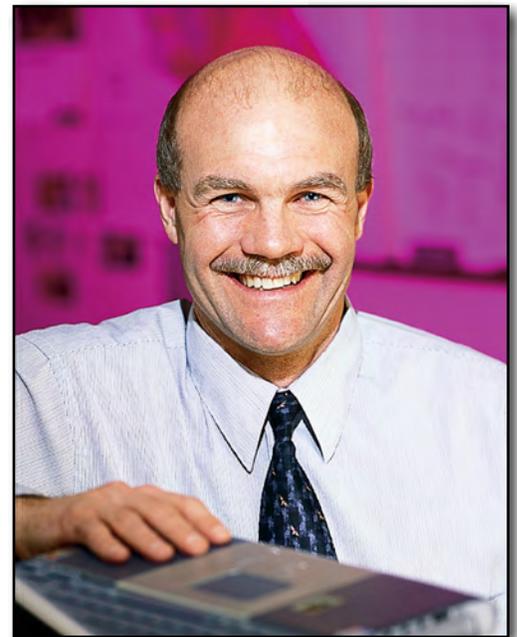
By Carl Marziali

A 20-year study, published March 5 in the New England Journal of Medicine, found that millennial children in Southern California breathe easier than ones who came of age in the 1990s. The University of Southern California (USC) [Children's Health Study](#), funded in part by NIEHS, measured lung development between the ages of 11 and 15 and found large gains for children studied from 2007 to 2011, compared to children of the same age, in the same communities, in the periods 1994-1998 and 1997-2001.

The gains in lung function paralleled improving air quality in the communities studied, and across the Los Angeles (LA) basin, as policies to fight pollution took hold.

By following more than 2,000 children in the same locations over two decades, and adjusting for age, gender, ethnicity, height, respiratory illness, and other variations, the study provided strong evidence that improved air quality by itself brings health benefits.

“We saw pretty substantial improvements in lung function development in our most recent cohort of children,” said lead author [James Gauderman, Ph.D.](#), professor of preventive medicine at USC.



Gauderman cautioned, “We can't get complacent, because not surprisingly, the number of vehicles on our roads is continually increasing. Also, the activities at the ports of LA and Long Beach, which are our biggest polluting sources, are projected to increase.” (Photo courtesy of the University of Southern California)

Linked video:
[Watch Gauderman discuss how children's lung function improved as the air in Southern California became cleaner. \(1:44\)](#)
(Launches in new window)

Download Media Player: Flash [↗](#)

“These solid scientific results demonstrate some of the ways that reducing air pollution provides significant health benefits to children, who are some of our most vulnerable citizens,” said Kimberly Gray, Ph.D., who oversees grants to the NIEHS/EPA Children's Environmental Health and Disease Prevention Research Centers.

Bigger lungs, better function

Combined exposure to two harmful pollutants, nitrogen dioxide (NO₂) and particulate matter with a diameter of less than 2.5 microns (PM_{2.5}), fell approximately 40 percent for the third cohort of 2007-2011 compared to the first cohort of 1994-1998. The study followed children from Long Beach, Mira Loma, Riverside, San Dimas, and Upland.

Children's lungs grew faster as air quality improved. Lung growth from age 11 to 15 was more than 10 percent greater for children breathing the lower levels of NO₂ from 2007 to 2011 compared to those breathing higher levels from 1994 to 1998.

The percentage of children in the study with abnormally low lung function at age 15 dropped from nearly 8 percent for the 1994-1998 cohort, to 6.3 percent in 1997-2001, to just 3.6 percent for children followed between 2007 and 2011 (see images on right).

The growing years are critical for lung development. The researchers are also monitoring lung function in a group of adults who participated in the study as adolescents. So far, they have not found evidence of a rebound after the teenage years. “Their lungs may have lost the opportunity to grow any more,” Gauderman suggested.

Broad benefits from better air

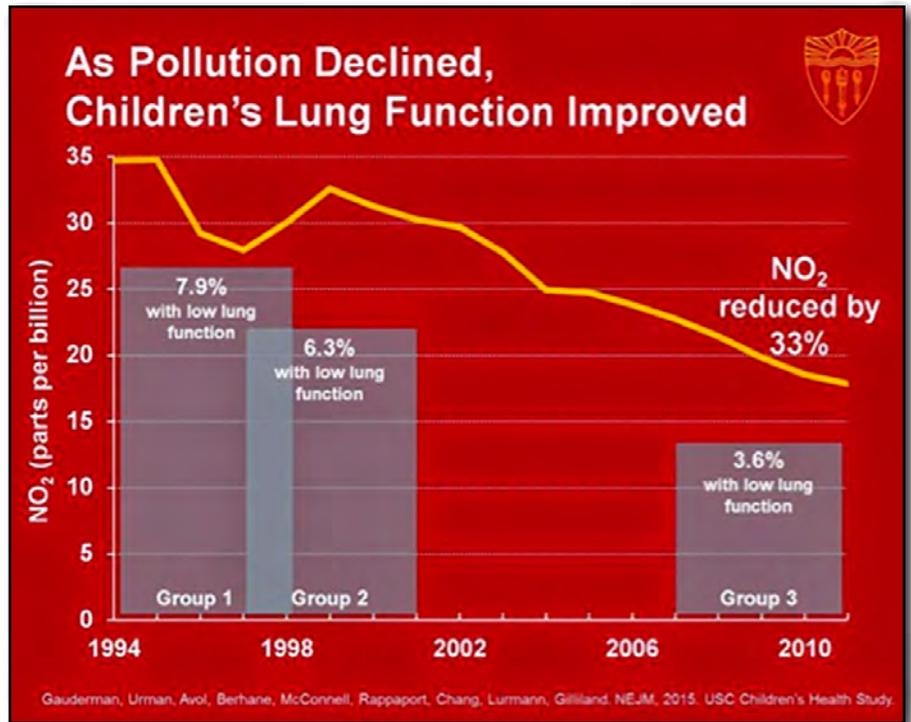
Across all five communities, lung development for children with asthma improved roughly twice as much as for other children. But even children without asthma showed significant improvements in their lung capacity, suggesting that all kids benefit from improved air quality.

“We expect that our results are relevant for areas outside southern California, since the pollutants we found most strongly linked to improved health — nitrogen dioxide and particulate matter — are elevated in any urban environment,” Gauderman said. “Our results suggest that better air quality in future will lead to even better lung health,” he said.

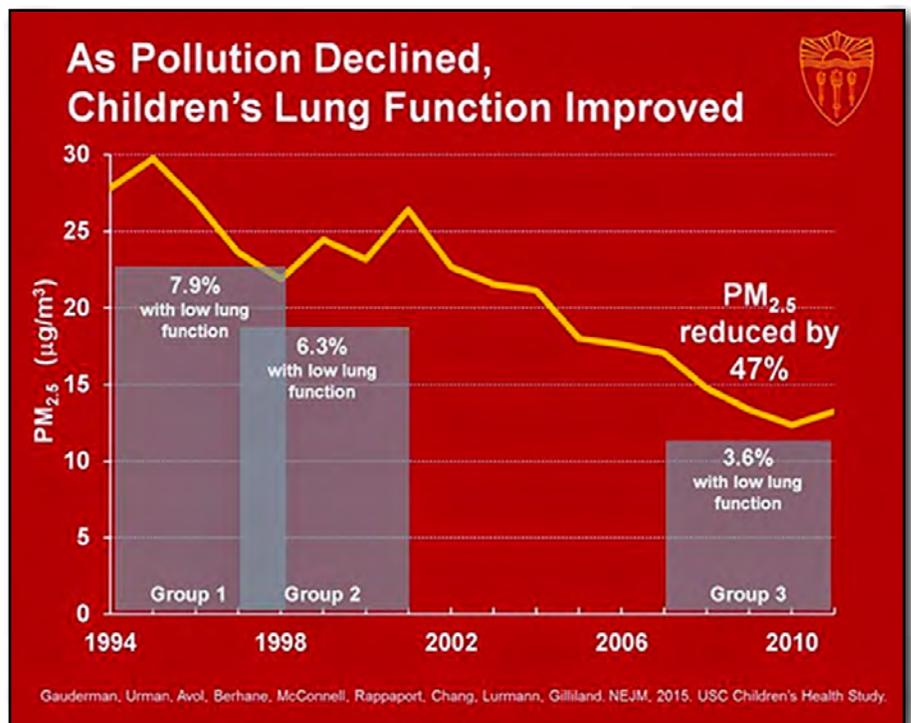
Citation: Gauderman WJ, Urman R, Avol E, Berhane K, McConnell R, Rappaport E, Chang R, Lurmann F, Gilliland F. 2015. Association of improved air quality with lung development in children. *N Engl J Med.* 372(10):905-913.

(Carl Marziali is assistant vice president for media and public relations at USC. This story is based on the USC press release.)

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[Click image to enlarge](#)



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Adelman makes key advance in understanding cell response to environmental cues

By Robin Arnette

Like runners passing a baton in a 4 x 100 meter relay race, networks within embryonic stem cells (ESCs) pass signals through a series of chemical reactions known as a signal transduction cascade. This pathway eventually turns on a particular gene or group of genes. The cues originate from the outside environment and tell ESCs to develop into a specific cell type, undergo self-renewal, or remain in a pluripotent state, which is the capability to turn into different cell types.

Signaling networks have long been recognized to be key regulators of ESC development, but NIEHS researcher Karen Adelman, Ph.D., and her group found a novel interplay between ESC signaling and transcription. This is the process in which DNA is transcribed into messenger RNA, which is the first step in generating functional gene products. She believes the work may explain what goes wrong when mammalian embryos fail to undergo a phenomenon called pausing. Her results appeared online March 12 in the journal *Molecular Cell*.



Adelman heads the Transcriptional Responses to the Environment Group in the NIEHS Epigenetics and Stem Cell Biology Laboratory. (Photo courtesy of Steve McCaw)

A new way of thinking

Adelman said that during transcription, RNA polymerase II (pol II) makes messenger RNA from DNA. A protein complex known as the negative elongation factor (NELF) induces pol II to pause shortly after it starts to synthesize RNA, during early transcription elongation. Several years ago, Adelman and her group found that the release of paused pol II into productive elongation is an important regulatory step that tunes the expression of a number of signal-responsive genes. They also determined that pausing governs the cell's ability to respond to environmental conditions.

However, her latest experiments told her that pausing did something essential in the early embryo. When she removed NELF from mouse cells, pol II failed to pause, and all of the mouse embryos died. She wondered what was happening.

“The accepted model in the field said pausing was keeping genes [that are] involved in differentiation turned off in the early embryo,” Adelman said. “That model predicted that if we abolished pausing, we’d see differentiation genes coming on, but we didn’t see that after doing the experiment several times.”

Even when Adelman added chemical signals that told the cells to differentiate, they failed to turn into different cell types. That is when she thought the standard model might not be entirely correct. Her data suggested that the ESCs were, in effect, not listening to the differentiation cues, because the signaling machinery had been repressed. In essence, when you get rid of pausing, you make ESC cells deaf to their environment (see graphic).

Results could be boon for regenerative medicine

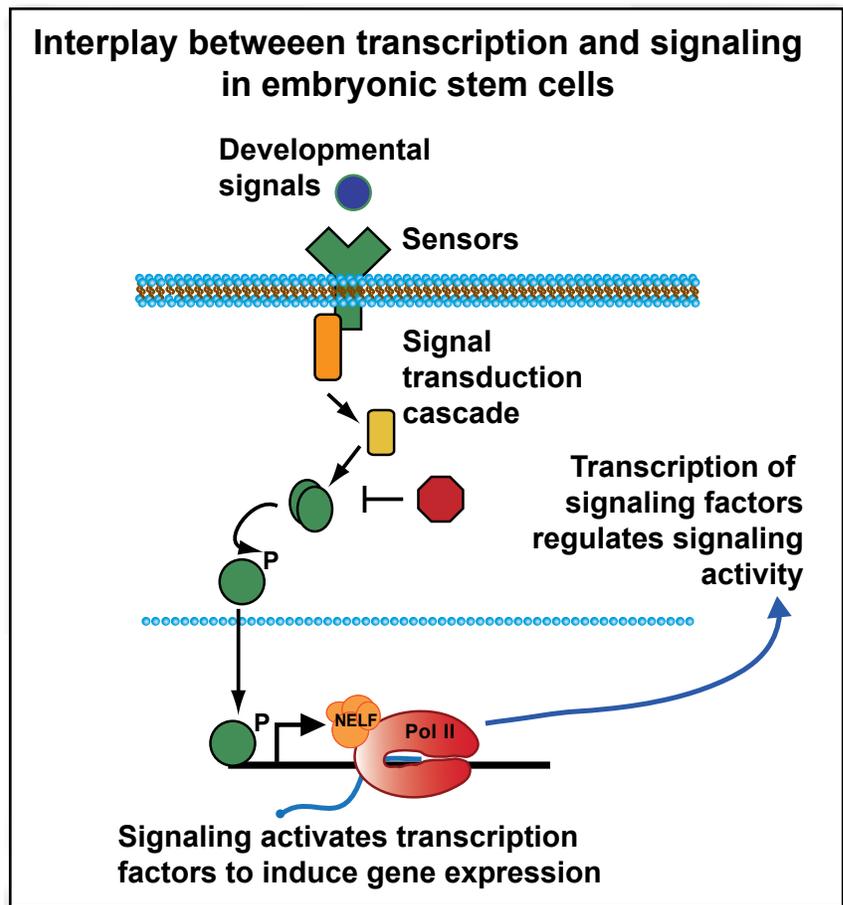
Adelman said the greatest potential for this research is in the field of regenerative medicine. In theory, she said, you can take a cell from a person with a heart condition, turn it into a pluripotent stem cell, and differentiate it into healthy heart tissue. But one of the current difficulties in that process is efficiently differentiating patient cells into the correct tissue type.

If researchers can get a handle on the signals that control pluripotency, they will know how to make a stem cell more or less sensitive to differentiation cues. The information will give them another tool.

When asked what the findings mean for transcription research, Adelman said there is an interplay between signal transduction and transcription, and that signaling is not always directive. Sometimes, it is responsive to the transcription machinery. Understanding how cells respond to environmental cues means taking that cross talk into account.

Citation: Williams LH, Fromm G, Gokey NG, Henriques T, Muse GM, Burkholder A, Fargo DC, Hu G, Adelman K. 2014. Pausing of RNA polymerase II regulates mammalian developmental potential through control of signaling networks. *Mol Cell*; doi:10.1016/j.molcel.2015.02.003 [Online 12 March 2015].

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The standard model shows the signaling components (black arrows) traveling to the nucleus (bottom of diagram) for transcription, but Adelman's work found that there is another signal coming back out of the nucleus (dark blue arrow). This signal tells the signaling machinery how much they are going to be transcribed, how abundantly, and how many copies per cell will be made. Adelman said you can increase cellular receptiveness to signals by increasing the concentration of signaling transcription factors. (Graphic courtesy of Karen Adelman)

Researchers tally substantial economic impact of EDC exposures

By Ernie Hood

What are endocrine disruptors?

Endocrine disruptors are chemicals that may interfere with the body's endocrine system and produce adverse developmental, reproductive, neurological, and immune effects in both humans and wildlife.

A wide range of substances, both natural and man-made, are thought to cause endocrine disruption, including pharmaceuticals, dioxin and dioxin-like compounds, polychlorinated biphenyls, DDT and other pesticides, and plasticizers, such as bisphenol A.

Endocrine disruptors may be found in many everyday products, including plastic bottles, metal food cans, detergents, flame retardants, food, toys, cosmetics, and pesticides.

An international group of researchers, including NIEHS scientist Jerry Heindel, Ph.D., and several NIEHS grantees, quantified the economic impact of health effects from exposures to endocrine-disrupting chemicals (EDCs) in the European Union (EU). The impact is considerable, despite conservative estimates. The scientists estimated that such exposures result in an annual median economic burden ranging from approximately \$165 billion (157 billion euros), or 1.23 percent of gross domestic product in the EU, up to \$256 billion (269 billion euros).

The authors published four papers March 5 in the *Journal of Clinical Endocrinology and Metabolism*. They selected three conditions with the strongest links to EDC exposure — obesity and diabetes, male reproductive disorders, and neurological effects. Three of the papers presented calculations associated with these conditions. The fourth article described the overarching methodologies and results of the project.

Conservative estimates and significant effects

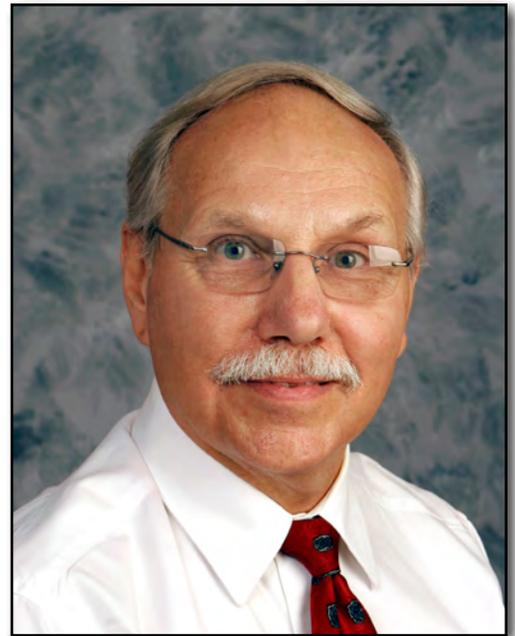
The researchers addressed exposures to specific chemicals, including bisphenol A, phthalates, flame retardants, organophosphate pesticides, and DDE, which is the breakdown product of the banned insecticide DDT. The strongest data indicated that exposures to pesticides could lead to the loss of 13 million IQ points across the EU, as well as 59,300 children being born each year with intellectual disabilities.

“The economic cost estimate is very conservative, [as it is] based on assessment of less than 5 percent of the known EDCs, and the fact that the economic costs do not consider all of the costs associated with these chronic conditions,” said [Jerry Heindel, Ph.D.](#), NIEHS health scientist administrator and one of the authors.

A wake-up call

The EU is developing regulations targeting EDCs, so the findings come at a good time to potentially influence policy. The conclusion of the authors is clear. “There is a substantial probability of very high disease costs across the life span associated with EDC exposure in the EU,” they said, noting that those high costs will accrue annually as long as exposures continue unchanged. “Regulatory action to limit exposure to the most widely prevalent and potentially hazardous EDCs is likely to produce substantial economic benefits,” the authors wrote.

Linda Birnbaum, Ph.D., director of NIEHS and the National Toxicology Program, called the new findings a wake-up call for policymakers and health experts. Although the results do not translate directly into estimates of EDC exposure impact in the U.S., Heindel said it is likely that U.S. findings would be similar. Birnbaum agreed. “If you applied these numbers to the U.S., they would be applicable, and in some cases higher,” she told [National Geographic](#).



Heindel administers the NIEHS grants program in endocrine disruptors, developmental basis of diseases, reproductive toxicology, and obesity. (Photo courtesy of Steve McCaw)



Trasande, shown at his 2014 NIEHS seminar, is a faculty member in pediatrics and environmental medicine at the NYU School of Medicine, and in health policy at the NYU Wagner Graduate School of Public Service. (Photo courtesy of Steve McCaw)

A new model for environmental health science decision-making

To perform their calculations, the researchers used methods previously developed by the Institute of Medicine, the World Health Organization, and the Intergovernmental Panel on Climate Change. “The approach we have taken will potentially transform decision-making in environmental health,” the authors wrote.

Heindel said that the group is working to complete two similar papers, addressing female reproductive health and endocrine cancers. He said it is likely the analyses will then expand to include the U.S. and more diseases.

Heindel and NIEHS grantee [Leonardo Trasande, M.D.](#), of New York University (NYU), started and organized the project, securing funding from organizations including the Endocrine Society. The publications were announced simultaneously at ENDO 2015, the organization’s annual meeting held in San Diego, and at a release event in Brussels.



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

Citations:

[Trasande L, Zoeller RT, Hass U, Kortenkamp A, Grandjean P, Myers JP, DiGangi J, Bellanger M, Hauser R, Legler J, Skakkebaek NE, Heindel JJ.](#) 2015. Estimating burden and disease costs of exposure to endocrine-disrupting chemicals in the European Union. *J Clin Endocrinol Metab*; doi:10.1210/jc.2014-4324 [Online 5 March 2015].

[Legler J, Fletcher T, Govarts E, Porta M, Blumberg B, Heindel JJ, Trasande L.](#) 2015. Obesity, diabetes, and associated costs of exposure to endocrine-disrupting chemicals in the European Union. *J Clin Endocrinol Metab*; doi:10.1210/jc.2014-4326 [Online 5 March 2015].

[Hauser R, Skakkebaek NE, Hass U, Toppari J, Juul A, Andersson AM, Kortenkamp A, Heindel JJ, Trasande L.](#) 2015. Male reproductive disorders, diseases, and costs of exposure to endocrine-disrupting chemicals in the European Union. *J Clin Endocrinol Metab*; doi:10.1210/jc.2014-4325 [Online 5 March 2015].

[Bellanger M, Demeneix B, Grandjean P, Zoeller RT, Trasande L.](#) 2015. Neurobehavioral deficits, diseases, and associated costs of exposure to endocrine-disrupting chemicals in the European Union. *J Clin Endocrinol Metab*; doi:10.1210/jc.2014-4323 [Online 5 March 2015].

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Pregnancy hormone plays a role in fetal response to hormone disruptors

By Kathleen Loudon

Early exposure in the human womb to phthalates, which are common environmental chemicals, disrupts the masculinization of male genitals, according to an NIEHS-funded study that was presented March 8 at the [Endocrine Society](#) meeting in San Diego. Phthalates are hormone-altering chemicals, called endocrine disruptors, and are found in many plastics, containerized foods, and personal care products.

The clinical study confirms similar results of animal studies and provides new information about how phthalates target a main pregnancy hormone, said the lead scientist, [Jennifer Adibi, Sc.D.](#), of the University of Pittsburgh. This hormone, known as human chorionic gonadotropin (hCG), is made during pregnancy by the placenta and can be measured in the mother’s blood and urine.

“The placenta, which is an extension of the fetus and a target of the chemicals in our bodies, broadcasts information early in pregnancy, through hCG, about what might be occurring to the fetus [from] chemical exposure,” Adibi said. “We may be able to act on this information to protect the pregnancy and the long-term health of the future child.”

“Jennifer’s research has potential to be paradigm changing, because she is investigating the role of the placenta in mediating the effects of endocrine disruptors during early human development,” said Thad Schug, Ph.D., who oversees NIEHS grants related to reproduction and the endocrine system.



Adibi is a promising early-stage researcher, funded through the NIH Pathway to Independence Award program. (Photo courtesy of Jennifer Adibi)



Linked video:
[Watch Jennifer Adibi, Sc.D., discuss her research on the effects of phthalates on the developing fetus in this University of Pittsburgh video. \(2:29\)](#)
(Launches in new window)

Download Media Player:  Flash [↗](#)

Linking phthalates, hCG, and human development

The researchers wanted to study whether phthalates disrupt male sexual differentiation and whether they do so by acting on hCG. They used an emerging biological marker of hormonal action *in utero*, the anogenital distance at birth, which is the distance between the anus and the genitals. Studies in male animals and in young men show that a longer anogenital distance correlates with better fertility and that a short anogenital distance is strongly associated with greater risk of a low sperm count.

Adibi and her co-workers used data from a multicenter NIEHS-funded study called The Infant Development and Environment Study, or **TIDES**, which studied a cohort of 780 pregnant women and their children from 2010 to 2013.

Sex-linked differences

By analyzing data from 362 women, Adibi and colleagues found that higher levels of hCG in the mothers’ blood were strongly associated with a shorter anogenital distance in male, but not female, babies.

Also, higher levels in mothers’ urine of two metabolites of a prevalent phthalate, mono-n-butyl phthalate and monobenzyl phthalate, were strongly associated with lower levels of hCG in women carrying male babies and with higher hCG levels in those carrying female babies.

Using an analytical method known as statistical causal inference, the investigators estimated the degree to which these chemicals affected anogenital distance by way of hCG. The researchers reported that in female babies, hCG explained about 8 percent of the effect of phthalates on the genitals, and in males, it was responsible for 20 to 30 percent. It is unclear why the effect varies by sex, Adibi said.

“Our study is the first to show that hCG is a target of phthalate exposure in early pregnancy and to confirm previous findings that it is a critical hormone in male development,” Adibi said. “Increased knowledge of placental hormones and their relationships to the baby’s health may one day improve our ability to detect fetal abnormalities earlier in pregnancy,” she said.

(Kathleen Loudon is a contract writer for the Endocrine Society. This story is based on the Endocrine Society [press release](#).)

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NTP hosts regional meeting to highlight juvenile toxicology

By *Natasha Catlin and Erin Quist*

Invited speakers from academia, industry, research organizations, and government came to NIEHS March 13 to share their unique perspectives and expertise in juvenile toxicology. Organized by members of the Society of Toxicologic Pathology Education Committee and the Reproductive Pathology Special Interest Group, the [regional meeting](#) highlighted toxicology in the morning and pathology challenges in the afternoon.

John Bucher, Ph.D., director of the NIEHS Division of the National Toxicology Program (NTP) opened the meeting with an overview of the program. “There has been a conceptual shift in environmental health sciences from the traditional view of overwhelming the body’s defense by brute force with high doses of chemicals, to [studying] the interactions of chemicals with hormonal systems,” he said.

Bucher pointed out that lower doses influence developmental patterns in more subtle ways. The shift in toxicological studies to look for health effects from perinatal exposures, rather than those in adolescence or adulthood, corresponds with the NIEHS strategic plan goal to study susceptibility across the life span.

Approaches to studying juvenile toxicology

David Peden, M.D., director of the Center for Environmental Medicine, Asthma, and Lung Biology, and head of the Division of Pediatric Allergy, Immunology, and Rheumatology at the University of North Carolina at Chapel Hill, established the importance of the day’s presentations.

“If clinicians are making decisions based on information that’s obtained at the wrong life stage, you may entirely miss major toxicities,” he said, citing the effects of thalidomide. Thalidomide was a sedative, marketed in the late 1950s and early 1960s, that was found to be effective for morning sickness, but unknowingly crossed the placenta causing thousands of birth defects and infant deaths.

Ikram Elayan, Ph.D., with the U.S. Food and Drug Administration (FDA), pointed out that juvenile toxicology studies are needed because traditional studies often fail to obtain data from infancy to adulthood. The choice of endpoints in a juvenile study should be informed by, but not defined by, the adult data, she said.

According to Robert Parker, Ph.D., with Huntingdon Life Sciences, a case-by-case approach to study design is called for. Studies should address all phases of growth and development, he said, as well as both on-target and off-target changes.



With contagious enthusiasm, Dixon, one of the meeting organizers, welcomed participants and thanked her co-organizers, Tom Steinbach, D.V.M, with EPL Inc., and Amera Remick, D.V.M, with WIL Research. (Photo courtesy of Steve McCaw)

LaRonda Morford, Ph.D., with WIL Research, noted that in pediatric drug development studies, pharmacological relevance must be established in the test species.

Pathology perspectives

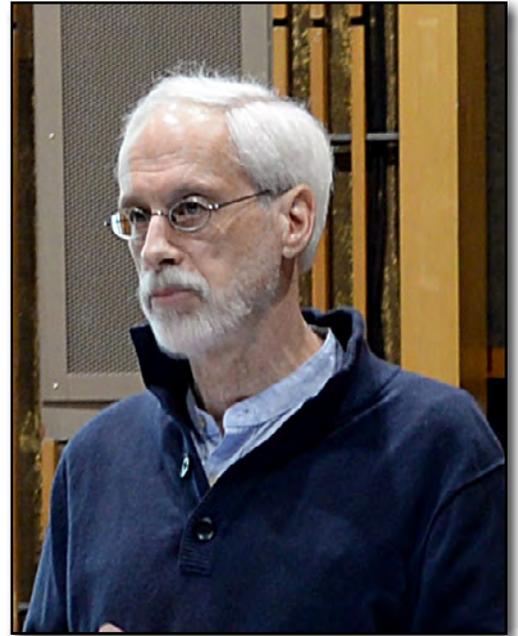
George Parker, D.V.M., Ph.D., of WIL Research, led off the afternoon session on pathology. Parker discussed challenges, such as postnatal tissue development and the lack of controls animals for those who die unexpectedly. Catherine Picut, V.M.D., J.D., also of WIL Research, reviewed histopathological changes observed in various tissues and organs at early developmental time points.

Toxicology of the developing kidney was addressed by John Seely, D.V.M., from Experimental Pathology Laboratories (EPL) Inc. He pointed out that differences in drug sensitivity are dependent upon the current stage of nephrogenesis, or kidney development, so juvenile nephrotoxicity cannot be estimated from adult data.

Mark Cline, D.V.M., Ph.D., from the Wake Forest School of Medicine, discussed using nonhuman primates, stressing the importance of managing variability, determining whether specific pathogens are present, and documenting objective indicators of age, such as tooth development.

Darlene Dixon, D.V.M., Ph.D., closed the meeting by underscoring the unique factors of juvenile studies. “The importance of studying perinatal and early life effects can’t be overstated,” she said.

(Natasha Catlin, Ph.D., is an Intramural Research and Training Award (IRTA) fellow in the Developmental and Reproductive Toxicology Group, and Erin Quist, D.V.M., is an IRTA fellow in both the NTP Pathology Group and Reproductive Endocrinology Group.)



Bucher gave an overview of NTP, highlighting refinements to traditional assays, including the modified one-generational study, which begins with perinatal dosing and follows all offspring into adulthood, looking at specific endpoints in different groups. (Photo courtesy of Norris Flagler)



Peden stressed the need to study early life exposure, saying that we have to study the correct life stage to understand the true effects of exposures. (Photo courtesy of Norris Flagler)



Elayan’s regulatory discussion of the FDA views on juvenile toxicity studies generated many questions from participants. (Photo courtesy of Norris Flagler)



Morford addressed pharmaceutical studies of small molecules and said that the rat is the preferred species for nonclinical evaluation of pediatric safety. (Photo courtesy of Norris Flagler)



From left, Margarita Gruebbel, D.V.M., Ph.D., EPL Inc.; Tom Steinbach, D.V.M., EPL, Inc.; and Danielle Brown, D.V.M., WIL Research, were among the 70 scientists who gathered for the regional meeting. Steinbach was one of the organizers. (Photo courtesy of Steve McCaw)



Picut presented a histology atlas of postnatal rat development. (Photo courtesy of Steve McCaw)



Discussing the pathology challenges of juvenile toxicity studies, Parker stressed the need for age-matched controls. (Photo courtesy of Steve McCaw)

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Wetterhahn winner uses native plants to stabilize arsenic in mine waste

By Sara Mishamandani

University of Arizona (UA) Superfund Research Program (SRP) graduate student Corin Hammond and an interdisciplinary group of scientists are experimenting with using native plants as an easy, cost effective, and sustainable method of stabilizing arsenic in mine waste. Hammond, winner of the 16th [Karen Wetterhahn Memorial Award](#), presented results and ongoing research from the waste stabilization project in a March 17 talk at NIEHS.

Hammond's doctoral work focuses on the [Iron King Mine and Humboldt Smelter Superfund site](#) near Dewey-Humboldt, Arizona. At the site, large piles of mine waste contain arsenic and other metals that that can spread through the air in dust, due to the region's arid conditions, and through water, from periodic flooding and runoff. To reduce exposure to arsenic, UA SRP scientists are studying the use of plants to stabilize contaminants from the mine waste and thus prevent transport to nearby communities.

Testing plant growth and stabilization potential

Hammond wants to know whether phytostabilization can prevent movement of arsenic from mine waste piles. To find out, Hammond and her team planted several types of plants, using different amounts of compost, on top of several mine waste piles. As the plants grow, Hammond's team collects soil cores from each plot to test whether the arsenic is becoming more tightly bound to particles in the soil.

Researchers chose native plants that can grow in the arid climate and acidic soil with a high metal content. They are also testing plants that do not accumulate arsenic in plant tissue, but instead stabilize metals in the root zone of the soil. This provides a longer-term solution, because it does not require harvesting the plants to remove arsenic from the area, and it poses less danger to animals that may eat the plants.

So far, Hammond's team has identified chemical processes that convert arsenic into stable products in the root zone of the plants. This shows that the plants may be helping to keep arsenic from moving through the soil and producing dust that contains arsenic.

A simple solution to a complicated problem

Sustainable management of waste is a challenge facing the mining industry worldwide. Capping or covering mine waste is often used to reduce or eliminate erosion, but it can be prohibitively expensive.



Hammond is a graduate student under the guidance of Jon Chorover, Ph.D., in the Department of Soil, Water, and Environmental Science at the UA College of Agriculture and Life Sciences. (Photo courtesy of Steve McCaw)



Bill Suk, Ph.D., director of the NIEHS Superfund Research Program, introduced Hammond and moderated the question and answer session. In his introductory remarks, he honored Karen Wetterhahn, Ph.D., a professor at Dartmouth College who died tragically in 1997 as a result of a laboratory accident. He emphasized that all of the award winners have followed in the footsteps of Wetterhahn as outstanding researchers and mentors. (Photo courtesy of Steve McCaw)

According to Hammond, this project is establishing the potential for plants to serve as a vegetative cap, which is a far more cost-effective method to reduce movement of arsenic from mine waste piles.

“We are looking for a simple solution to a very complicated problem,” said Hammond. “The project requires scientists from a wide range of disciplines, and long-term studies, to explore the interactions between plants and the characteristics of the mine waste during the vegetation process.”

(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.)



Hammond highlighted efforts to partner with industry to move this work forward. The research sparked an industry-university cooperative, the Center for Environmentally Sustainable Mining, that is bringing researchers together with the mining industry to examine environmental stewardship of mining sites. (Photo courtesy of Steve McCaw)



Attendees included, from left, NIEHS and National Toxicology Program Director Linda Birnbaum, Ph.D.; NIEHS health scientist administrator Michelle Heacock, Ph.D.; and Mark Miller, Ph.D., NIEHS chief of staff. (Photo courtesy of Steve McCaw)

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NIEHS scientists stand out at TCRB meeting

By Shannon Whirledge

The Triangle Consortium for Reproductive Biology (TCRB) held its 24th annual meeting March 14 at NIEHS in Research Triangle Park. Researchers and trainees from throughout North Carolina came together to exchange scientific knowledge on many aspects of mammalian reproduction.

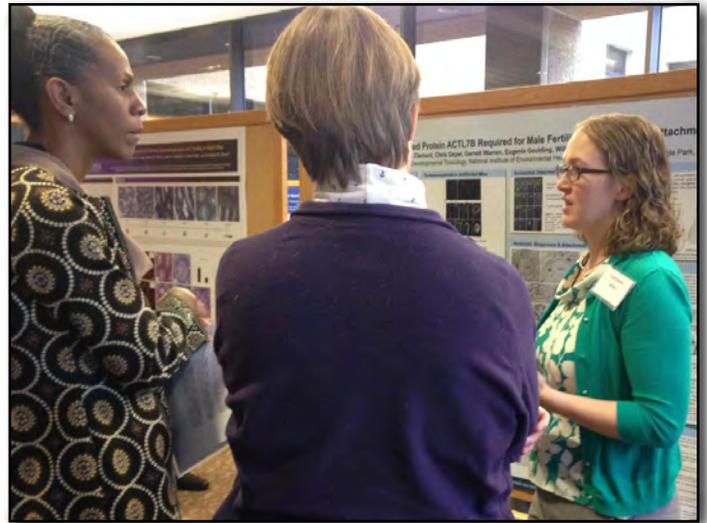
NIEHS scientists made a strong showing at the event. Janet Hall, M.D., with the NIEHS clinical research program, gave one of three invited presentations. Also, three of the four trainee posters chosen for oral presentation were by NIEHS fellows (see [text box](#)).

Carmen Williams, M.D., Ph.D., head of the NIEHS Reproductive Medicine Group, emphasized the value of trainees meeting with regional researchers. “It’s a great experience for trainees to get feedback from peers, locally,” she said. “It helps them prepare for more formal conferences and interviews, as well.”

Vitamin D affects pregnancy outcomes

Genevieve Neal-Perry, M.D., Ph.D., from the University of Washington, delivered the keynote address, discussing her work on vitamin D deficiency and reproductive success. She noted that deficiency is prevalent in the U.S., affecting two out of three women.

Neal-Perry has found that chronic deficiency in mice leads to reduced fertility, in part through increases in oxidative stress in ovaries and poor health of egg cells. Vitamin D deficiency has also been linked to polycystic ovarian syndrome, infertility, recurrent pregnancy loss, and infants born small for gestational age.



Neal-Perry, left, and Williams, center, listened as Tracy Clement, Ph.D., described her work during one of the poster sessions. Clement is a research fellow in the NIEHS Gamete Biology Group. (Photo courtesy of Shannon Whirlledge)

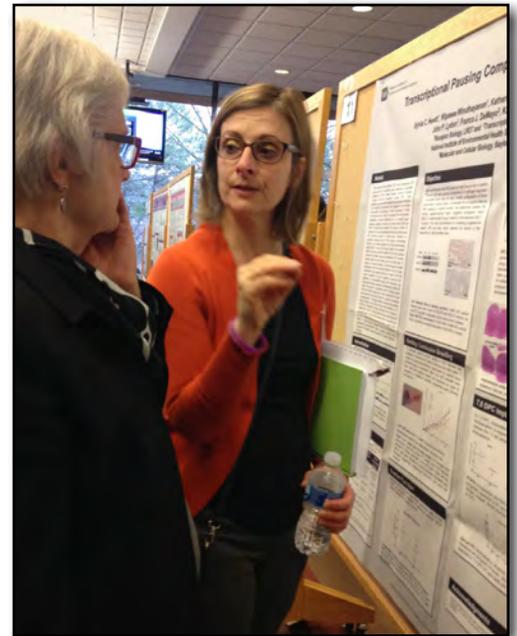
Provocative presentations by regional researchers

Three regional researchers shared thought-provoking presentations. Anne Steiner, M.D., associate professor at the University of North Carolina at Chapel Hill (UNC), shared her work on the UNC [Time to Conceive](#) study. By following women as they attempt to conceive, Steiner has been able to assess biomarkers that can predict a woman's reproductive potential and examine exposures that may negatively impact female fertility.

Jay Kaplan, Ph.D., professor of pathology and translational medicine at Wake Forest University, and Hall both spoke on changes in women's health associated with aging.

According to Hall, women have increased risk for depression and cognitive deficits during the perimenopausal period, due to changing ovarian hormones. Using neuroimaging studies, she has found that the timing of estrogen replacement is critical. The activation of key regions involved in working memory and executive function is significantly greater in perimenopausal women receiving long-term treatment, suggesting women and doctors may need to take a proactive approach to hormone replacement.

Kaplan noted that menopause and the corresponding changes in ovarian hormones are associated with sex differences in prevalence of cardiovascular disease. Kaplan took issue with the view that women are protected by hormones from coronary artery disease and atherosclerosis. Instead, he said, "women are not protected, just delayed." His studies have shown that ovarian dysfunction and psychological stress in the premenopausal period can promote progression of early coronary artery atherosclerosis.



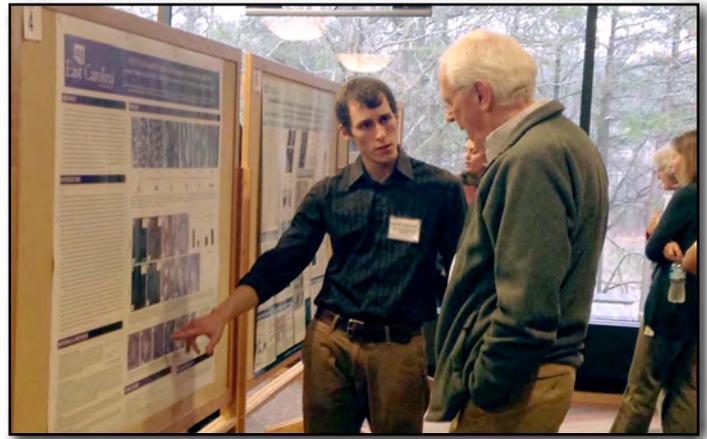
Sylvia Hewitt, right, senior biologist in the NIEHS Receptor Biology Group, explained her evaluation of transcriptional pausing in uterine physiology to Phyllis Leppert, M.D., Ph.D., a member of the Champion Fund's board of directors. (Photo courtesy of Shannon Whirlledge)

NIEHS trainees shine during poster presentations

For the second year, the [Campion Fund](#), supported by The Phyllis and Mark Leppert Foundation for Fertility Research, provided awards for best oral and poster presentation, and for the second time, both awardees were NIEHS trainees.

Alisa Suen was selected for the best oral presentation (see [text box](#)), and Kristen Upson, Ph.D., a postdoctoral fellow in the NIEHS Women's Health Group headed by Donna Baird, Ph.D., won for best poster.

(Shannon Whirlledge, Ph.D., is an Intramural Research Training Award fellow in the NIEHS Molecular Endocrinology Group.)



Besides presenters and award winners, other NIEHS scientists participated in the event. Mitch Eddy, Ph.D., head of the NIEHS Gamete Biology Group, listened as Jonathan Busada, a graduate student at East Carolina University, explained his research. (Photo courtesy of Sylvia Hewitt)

Oral presentations by NIEHS trainees

Barbara Nicol, Ph.D., presented “Gonadal Identity in the Absence of Pro-Testis Factor SOX9 and Pro-Ovary Factor β -Catenin.” She was one of three National Institutes of Health (NIH) fellows selected for the prestigious WSA Scholar award by the NIH Women Scientist Advisors (WSA) Committee, and she presented a lecture on her research March 20 at NIH in Bethesda, Maryland. Nicol works in the NIEHS Reproductive Developmental Biology Group headed by Humphrey Yao, Ph.D.

Ajeet Singh, Ph.D., presented “Brg1-Inactivation After Implantation Induced Apoptosis and Growth-Arrest.” He is a visiting fellow in the NIEHS Chromatin and Gene Expression Group led by Trevor Archer, Ph.D.

Alisa Suen presented “Aberrant SIX1 Expression May Contribute to the Development of Uterine Adenocarcinoma Following Neonatal Xenoestrogen Exposure,” which won best oral presentation. She is a predoctoral fellow in the NIEHS Reproductive Medicine Group headed by Carmen Williams, M.D., Ph.D.

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This month in EHP

The April issue of Environmental Health Perspectives (EHP) looks into the effects of climate change on *Vibrio*, a strain of pathogenic bacteria, and international policy initiatives to curb plastic waste in the world's oceans.

Warming Trend — How Climate Shapes *Vibrio* Ecology

Fluctuations in climate can powerfully affect the ecology and distribution of *Vibrio* bacteria. For example, a 1997 outbreak of *Vibrio parahaemolyticus* infections in coastal Peru followed elevated sea temperatures associated with the El Nino current. New studies are exploring, in greater depth, how elements of climate change are influencing the ecology of these pathogenic bacteria.



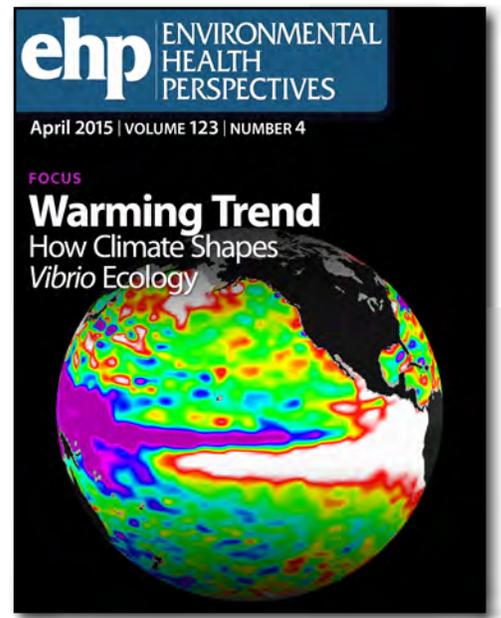
<http://twitter.com/ehponline>

Managing Marine Plastic Pollution — Policy Initiatives to Address Wayward Waste

There is growing urgency among industry, government, nongovernmental organizations, and environmental groups to develop tools and policies for tracking, capturing, and recycling plastic waste before it gets into the ocean. Economic and industry initiatives in Europe, China, and the United States are taking aim at responsible management of plastic pollution.

Featured research and related news articles this month include:

- **Air Pollution and Neonatal Blood Pressure: Examining Earlier Exposures** — Some studies have associated ambient air pollution with increased blood pressure in adults and children. New research examines exposures during gestation and reports a small, but significant, increase in newborn systolic blood pressure. The increase is associated with prenatal exposure, in the third trimester, to black carbon and, to a lesser extent, fine particulate matter.
- **New Tool for EDC Research: *In Vivo* Assay Screens for Estrogenic Effects** — High-throughput *in vitro* assays can help with preliminary screening of potential endocrine-disrupting compounds, but they can't identify how a compound may affect the body. Researchers describe a new *in vivo* screen they believe will improve efforts to identify high-priority chemicals for further study.
- **Dust Emissions From Cattle Feed Yards: A Source of Antibiotic Resistance?** — Scientists examine the extent to which five commonly used antibiotics, together with antibiotic-resistance genes and certain microbes, disperse from large-scale cattle feed yards via airborne particulate matter.
- **Urinary Biomarkers as Exposure Surrogates: Controlling for Possible Bias** — Biomonitoring can help identify human health risks associated with environmental exposures, but the accuracy of conclusions hinges on the correct interpretation of the data. A new study highlights a potential source of bias in estimating exposures on the basis of urine samples and suggests a possible means to control for it.



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GEMS spring meeting to feature NIEHS scientists and grantees

By Kelly Lenox

The Genetics and Environmental Mutagenesis Society (GEMS) has announced the program for its April 27 spring meeting and NIEHS will play a prominent role. Stephanie Smith-Roe, Ph.D., GEMS president-elect and genetic toxicologist in the National Toxicology Program (NTP) at NIEHS, will introduce the speakers, and current GEMS president, Channa Keshava, Ph.D., from the U.S. Environmental Protection Agency (EPA), will give the welcome.

**GEMS Fall Meeting —
save the date!**

When: October 28, 2015

Where: North Carolina
Biotechnology Center

The meeting, “Understanding How Genetic Variation Modifies Responses to Environmental Exposures,” will be held on the EPA campus in Research Triangle Park, North Carolina. Speakers include two NTP special volunteers, Jef French, Ph.D., and Mike Shelby, Ph.D.; NIEHS lead scientist Stephanie London, M.D., Dr.P.H.; and two NIEHS grantees, Samir Kelada, Ph.D., and Trudy Mackay, Ph.D.

More details and registration information are available on the [GEMS website](#).

GEMS presenters

Jef French, Ph.D., NTP special volunteer and adjunct professor at the University of North Carolina at Chapel Hill (UNC) — **Using Diversity Outbred Mice to Identify the Genetic Basis for Toxicity Thresholds and Susceptibility**

Samir Kelada, Ph.D., assistant professor, UNC — **Genetics of Environmentally-Induced Airway Disease in the Collaborative Cross Mouse Population**

Mike Shelby, Ph.D., NTP special volunteer — **A Tribute for Frederick J. de Serres, Ph.D.**

Trudy Mackay, Ph.D., professor, North Carolina State University — **Genetic Architecture of Environmental Susceptibility: Lessons From *Drosophila***

Stephanie London, M.D., Dr.P.H., NIEHS lead researcher — **Smoking and the Epigenome Across the Lifecourse**

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Extramural papers of the month

By Nancy Lamontagne

- [Roadmap epigenomics program maps more than 100 types of cells and tissues](#)
- [Pesticide exposure linked with ADHD behaviors in mice and people](#)
- [Mercury may be linked with autoimmune disorders](#)
- [Parental smoking during pregnancy linked with later diabetes in children](#)

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

Roadmap epigenomics program maps more than 100 types of cells and tissues

Researchers supported by the National Institutes of Health Common Fund Roadmap Epigenomics Program, which is co-led by NIEHS, have mapped the epigenomes of more than 100 types of human cells and tissues. This information can help scientists understand how changes to the genome and epigenome can lead to conditions such as Alzheimer’s disease, cancer, asthma, and fetal growth abnormalities.

Epigenetic changes are chemical modifications to DNA that alter how genes are expressed, without changing the genetic code. The epigenome contributes to unique gene expression and biological functions, and thus, unlike the genome, can vary among different cells and tissues. To better understand how the epigenome contributes to cell function as well as human disease, the researchers integrated information about histone marks, DNA methylation, DNA accessibility, and RNA expression to produce high-resolution maps of gene regulatory elements across 127 reference epigenomes — 111 from the Roadmap Epigenomics Program and 16 from the Encyclopedia of DNA Elements project — spanning diverse cell and tissue types.

The resulting comprehensive catalog of epigenomic data provides a first-of-its-kind resource that will help researchers make direct comparisons across cell types and tissues. The researchers expect that the data, which is freely available, will be of broad use to scientists for studies of gene regulation, cellular differentiation, genome evolution, genetic variation, and human disease. More than 20 additional papers, published in *Nature* and *Nature*-associated journals, show how these maps can be used to study human biology.

Citation: Roadmap Epigenomics Consortium, Kundaje A, Meuleman W, Ernst J, Bilenky M, Yen A, Heravi-Moussavi A, Kheradpour P, Zhang Z, Wang J, Ziller MJ, Amin V, Whitaker JW, Schultz MD, Ward LD, Sarkar A, Quon G, Sandstrom RS, Eaton ML, Wu YC, Pfenning AR, Wang X, Claussnitzer M, Liu Y, Coarfa C, Harris RA, Shores N, Epstein CB, Gjoneska E, Leung D, Xie W, Hawkins RD, Lister R, Hong C, Gascard P, Mungall AJ, Moore R, Chuah E, Tam A, Canfield TK, Hansen RS, Kaul R, Sabo PJ, Bansal MS, Carles A, Dixon JR, Farh KH, Feizi S, Karlic R, Kim AR, Kulkarni A, Li D, Lowdon R, Elliott G, Mercer TR, Neph SJ, Onuchic V, Polak P, Rajagopal N, Ray P, Sallari RC, Siebenthal KT, Sinnott-Armstrong NA, Stevens M, Thurman RE, Wu J, Zhang B, Zhou X, Beaudet AE, Boyer LA, De Jager PL, Farnham PJ, Fisher SJ, Haussler D, Jones SJ, Li W, Marra MA, McManus MT, Sunyaev S, Thomson JA, Tlsty TD, Tsai LH, Wang W, Waterland RA, Zhang MQ, Chadwick LH, Bernstein BE, Costello JF, Ecker JR, Hirst M, Meissner A, Milosavljevic A, Ren B, Stamatoyannopoulos JA, Wang T, Kellis M. 2015. Integrative analysis of 111 reference human epigenomes. *Nature* 518(7539):317-330. (See [story](#).)

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Pesticide exposure linked with ADHD behaviors in mice and people

NIEHS-funded research in humans and mice provides new evidence that early exposure to the commonly used pyrethroid pesticide, deltamethrin, may be a risk factor for attention-deficit hyperactivity disorder (ADHD).

Although there is strong scientific evidence that genetics plays a role in susceptibility to ADHD, no single gene has been linked to a significant percentage of cases, leading scientists to believe that environmental factors may also contribute to development of the disorder. To mimic exposures in pregnant women, the researchers exposed female mice to deltamethrin during pregnancy and lactation. The pups exhibited features of ADHD, including hyperactivity, impulsive behavior, and problems with working memory and attention. Similar to what is seen in children with ADHD, the male mice were more affected than females. And ADHD-like behaviors in the mice lasted through adulthood, even though the pesticide could no longer be detected in their systems. The researchers also observed increased dopamine transporter and receptor levels in the pups, which they say are likely to be responsible for the ADHD-like behaviors.

The researchers also looked at pyrethroid pesticide exposure in children, using data from the National Health and Nutrition Examination Survey. An analysis of health care questionnaires and urine samples from 2,123 children and adolescents revealed that children with higher pyrethroid pesticide metabolite levels in their urine were more than twice as likely to be diagnosed with ADHD.

Citation: Richardson JR, Taylor MM, Shalat SL, Guillot TS 3rd, Caudle WM, Hossain MM, Mathews TA, Jones SR, Cory-Slechta DA, Miller GW. 2015. Developmental pesticide exposure reproduces features of attention deficit hyperactivity disorder. *FASEB J*; doi:10.1096/fj.14-260901 [Online 28 January 2015].

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Mercury may be linked with autoimmune disorders

NIEHS grantees report an association between exposure to methylmercury — even at levels generally considered safe — and the development of autoimmunity, which can sometimes lead to autoimmune diseases, such as inflammatory bowel disease, lupus, rheumatoid arthritis, and multiple sclerosis.

Autoimmunity occurs when the immune system begins treating normal proteins in the body as if they are foreign invaders. To study mercury's effects on autoimmunity, the researchers analyzed data from 1,352 women ages 16-49 who participated in the National Health and Nutrition Examination Survey from 1999 to 2004. They assessed mercury levels based on hair and blood samples, which can be used to track organic mercury, or methylmercury, exposure, as well as urine samples, which can be used to track inorganic mercury.

Tests revealed the presence of antinuclear antibodies (ANA), a marker of autoimmunity, in 16 percent of the study participants. The researchers found an association between ANA levels and mercury levels in hair and blood, but not urine, after adjusting for confounders. The association was strongest for the women with the highest ANA levels. However, even at low methylmercury levels — less than 0.37 parts per million hair mercury and less than one microgram per liter blood mercury — the researchers observed a dose-response relationship. The researchers note that these levels are in the range that regulatory agencies generally consider safe for women of childbearing age.

The new findings point to the need for further investigation into the relationship between methylmercury and autoimmune conditions.

Citation: Somers EC, Ganser MA, Warren JS, Basu N, Wang L, Zick SM, Park SK. 2015. Mercury exposure and antinuclear antibodies among females of reproductive age in the United States: NHANES. *Environ Health Perspect*; doi: 10.1289/ehp.1408751 [Online 10 February 2015].

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Parental smoking during pregnancy linked with later diabetes in children

A study, funded in part by NIEHS, found that women with parents who smoked during pregnancy had an increased risk for developing diabetes as adults, independent of their birth weight and current body mass index (BMI).

The researchers analyzed data from 1,801 daughters of women who participated in the Child Health and Development Studies, an ongoing project of the Public Health Institute. The daughters, ages 44-54 years old at the time of analysis, were two to three times more likely to have diabetes as adults if their mothers smoked

while pregnant. The association remained after adjustment for parental race, diabetes, and employment. Dads who smoked while their daughter was *in utero* also contributed to an increased diabetes risk for their child, but to a lesser extent than the mothers. The effect of parental smoking was unchanged when adjusted for daughters' birth weight and current BMI, both of which are risk factors for diabetes.

The data set was originally collected to study early risk of breast cancer, which is why sons are not included. The results provide further evidence that pregnant women should avoid smoking or being around cigarette smoke.

Citation: La Merrill MA, Cirillo PM, Krigbaum NY, Cohn BA. 2015. The impact of prenatal parental tobacco smoking on risk of diabetes mellitus in middle-aged women. *J Dev Orig Health Dis*; doi:10.1017/S2040174415000045 [Online 10 February 2015].

(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 Tara Ann Cartwright, John House, Vijay More, and Qing Xu

- [NIEHS researchers introduce sensitive tool to track replication enzymology](#)
- [A Notch or two in ozone susceptibility](#)
- [Plasma antioxidants are not feasible biomarkers of endotoxin-induced oxidative damage](#)
- [Poly beta and FEN1 perform a complementation role in APTX-deficient cells](#)

NIEHS researchers introduce sensitive tool to track replication enzymology

In a recent paper published in *Nature Structural and Molecular Biology*, NIEHS researchers and their collaborators demonstrated a novel high-resolution method for tracking *in vivo* replication enzymology. Taking advantage of ribonucleotide inclusion in eukaryotic DNA as markers of replication, they devised a new 5' DNA end-mapping method, called hydrolytic end sequencing (HydEn-seq).

Researchers encoded ribonucleotide excision repair (RER)-deficient and RER-proficient yeast strains for wild type or variant DNA polymerase, with differential ribonucleotide inclusion abilities. They subjected genomic DNA from these strains to alkaline hydrolysis, then prepared libraries of single-stranded DNA fragments for Illumina HiSeq2500 sequencing.

The HydEn-seq technique could be applicable to enzymatic DNA hydrolysis or other lesions in DNA. The authors also project the usefulness of this technique for sensing polymerization changes due to endogenous or exogenous environmental stress. Moreover, with the availability of engineered replicases favoring ribonucleotide inclusion, HydEn-seq could also be made applicable to identifying replication origins, termination zones, and polymerase usage in organisms besides yeast. **(VM)**

Citation: Clausen AR, Lujan SA, Burkholder AB, Orebaugh CD, Williams JS, Clausen MF, Malc EP, Mieczkowski PA, Fargo DC, Smith DJ, Kunkel TA. 2015. Tracking replication enzymology in vivo by genome-wide mapping of ribonucleotide incorporation. *Nat Struct Mol Biol* 22(3):185-191.

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A Notch or two in ozone susceptibility

According to NIEHS scientists, mice deficient in either the Notch3 or Notch4 gene exhibited an increased immune response following an ozone-induced airway injury. The work is of vital importance, because ozone, which is one of the major components of smog, is involved in airway inflammation and exacerbation of existing airway diseases, including asthma and chronic obstructive airway disease.

To understand how genetic variation in humans may affect susceptibility to ozone-induced airway inflammation, the research team followed up on prior work that identified, in mice, a region on chromosome 17 associated with ozone-induced pulmonary inflammation. This region included Notch3 and Notch4, two genes known for their roles in development and cell fate decisions.

The researchers found that after ozone injury, the increased immune response displayed by Notch3- or Notch4-deficient mice was characterized by increases in lung permeability, lung neutrophils, and expression of Tnf when compared to similarly exposed wild type mice. In addition, transcriptome analysis revealed important differentially expressed genes, by genotype, related to inflammatory pathways.

This novel work identifies Notch3 and Notch4 genes as susceptibility genes for ozone-induced pulmonary injury, and suggests that Notch receptors, in addition to their well-characterized developmental functions, also function to modulate inflammatory innate immune responses to the environmental toxicant ozone. **(JH)**

Citation: Verhein KC, McCaw Z, Gladwell W, Trivedi S, Bushel PR, Kleeberger SR. 2015. Novel roles for Notch3 and Notch4 receptors in gene expression and susceptibility to ozone-induced lung inflammation in mice. *Environ Health Perspect*; doi:10.1289/ehp.1408852 [Online 6 February 2015].

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Plasma antioxidants are not feasible biomarkers of endotoxin-induced oxidative damage

NIEHS researchers and collaborators report that plasma antioxidants fail to measure the response to oxidative stress induced by endotoxin lipopolysaccharide (LPS). The study provides the latest information on the NIEHS Biomarkers of Oxidative Stress (BOSS) initiative.

The goal of the BOSS initiative is to test if certain blood products could be used as noninvasive indicators of oxidative stress that is involved in various human diseases. Previous studies exposing rats to ozone or to liver-damaging carbon tetrachloride were unable to validate plasma antioxidants as effective markers in those models.

To investigate the change of plasma antioxidants after endotoxin-induced oxidative stress, researchers in this study used the inflammatory LPS to treat Gottingen mini-pigs. Compared to rodents, pigs respond more like humans and serve as their own pretreatment controls. The scientists injected animals with two doses of LPS (2.5 and 5 micrograms/kilogram) and collected blood at four time points (2, 16, 48, and 72 hours). Several plasma antioxidants including ascorbic acid, uric acid, vitamin E, glutathione, and total antioxidant capacity were quantified. Though LPS induced tissue damage, as expected, no significant loss of plasma antioxidants was identified. The data add to the previous findings that plasma antioxidants are not a feasible measurement of oxidative stress. **(QX)**

Citation: Kadiiska MB, Peddada S, Herbert RA, Basu S, Hensley K, Jones DP, Hatch GE, Mason RP. 2015. Biomarkers of oxidative stress study VI. Endogenous plasma antioxidants fail as useful biomarkers of endotoxin-induced oxidative stress. *Free Radic Biol Med* 81:100-106.

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Poly beta and FEN1 perform a complementation role in APTX-deficient cells

Researchers from NIEHS have examined an alternative mechanism in which two base excision repair (BER) enzymes — DNA polymerase beta (pol beta) and flap endonuclease 1 (FEN1) — coordinate to remove the 5'-adenylated-deoxyribose phosphate (5'-AMP-dRP) group from BER intermediates in aprataxin (APTX)-deficient cells. APTX removes 5'-AMP-dRP from DNA following abortive ligation attempts by DNA ligase, thereby permitting later repair attempts to protect genomic integrity. APTX mutations cause the autosomal recessive neurodegenerative disease ataxia with oculomotor apraxia type I (AOAI).

The study used whole cell extracts, derived from APTX-null chicken DT40 cells and APTX-deficient AOAI human lymphocytes, to demonstrate that the enzymatic activities of pol beta and FEN1 were strong enough to substitute for APTX activity. The robust activity of pol beta and FEN1 in resolving 5'-AMP-dRP-containing BER intermediates also required coordination with each other. This study also showed that other enzymes with dRP lyase activity, such as DNA pol lambda, pol iota, pol theta, and Ku70, removed 5'-AMP-dRP groups from BER intermediates, but had minimal activity compared with those of pol beta and FEN1.

Taken together, this work highlights the impact of pol beta and FEN1 in the removal of adenylated BER intermediates in the absence of APTX activity. Additional studies are needed to understand how these BER enzymes influence disease phenotypes associated with APTX deficiency. **(TAC)**

Citation: Caglayan M, Horton JK, Prasad R, Wilson SH. 2015. Complementation of aprataxin deficiency by base excision repair enzymes. *Nucleic Acids Res* 43(4):2271-2281.

(Tara Ann Cartwright, Ph.D., is a former postdoctoral fellow in the NIEHS Intracellular Regulation Group. John House, Ph.D., is an Intramural Research Training Award (IRTA) fellow in the NIEHS Genetic Epidemiology Group. Vijay More, Ph.D., is a visiting fellow in the NIEHS Intracellular Regulation Group. Qing Xu is a biologist in the NIEHS Metabolism, Genes, and Environment Group.)

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Inside the Institute

NTP trainees get practical support before SOT

By Kelly Lenox

Following in the footsteps of the successful 2014 flash mentoring and poster session (see [story](#)), scientists in the National Toxicology Program (NTP) helped predoctoral and postdoctoral trainees prepare for the 2015 Society of Toxicology (SOT) annual meeting with a March 16 speed interviewing and scientific poster session.

Building on success

“Several mentors volunteered to do it again, which was great, because we were only taking volunteers,” said planning team member Sue Fenton, Ph.D., smiling. “And several mentees who couldn’t be here last year were first in line,” added Angela King-Herbert, D.V.M., also on the planning committee. Other planning team members included Darlene Dixon, D.V.M., Ph.D.; Michelle Hooth, Ph.D.; and Nigel Walker, Ph.D.

The team planned both a speed interviewing and poster session, to help trainees prepare for the brief discussions and actual interviews they will have at SOT. Speed interviewing was a practical choice, said Fenton, who emceed the session, because 60 percent of managers form their opinion of a job candidate within 10 minutes.

Practical experience

The planning team prepared questions and each interviewer randomly selected one to ask of the interviewees. The trainees had 5 1/2 minutes at each station — one minute to introduce themselves, and the remainder to answer the question.

The fast-paced sessions were followed by a debriefing, in which trainees and mentors shared what they learned. Trainees voiced a consensus that the hardest questions included being asked to explain their work to a fifth grader, and to name the qualities that set them apart from other candidates. They were much more comfortable with questions such as whether they preferred working on a team or individual basis.

The day ended with a scientific poster session, which gave trainees practice explaining their research to NIEHS and NTP staff — this time at a level a little higher than fifth grade.

Interviewers

- Raj Chhabra, Ph.D.
- Mike Devito, Ph.D.
- Darlene Dixon, D.V.M., Ph.D.
- June Dunnick, Ph.D.
- Michelle Hooth, Ph.D.
- Scott Masten, Ph.D.
- Andy Rooney, Ph.D.
- Greg Travlos, D.V.M.
- Nigel Walker, Ph.D.

Interviewees

- Sheba Churchill, D.V.M.
- Adam Filgo
- Olive Ngalame, Ph.D.
- Tanasa Osborne, D.V.M., Ph.D.
- Katie Pelch, Ph.D.
- Jessica Proctor
- Erin Quist, D.V.M.
- Kristen Ryan, Ph.D.
- Deirdre Tucker



Masten, left, listened to Ngalame as she described her feelings about working on a team vs. individually. During the debriefing, he said some of the best answers from participants included being energized by a team environment, liking the opportunity to learn from others who had skills they didn't, and appreciating teamwork because it enabled greater achievement. (Photo courtesy of Kelly Lenox)



Fenton's good humor helped keep the speed interviewing session moving on schedule. (Photo courtesy of Steve McCaw)



Walker, left, asked Pelch and others to share a time they solved a problem. Several mentors echoed the theme that specific stories were far more memorable answers than general responses. (Photo courtesy of Kelly Lenox)



During the poster session, King-Herbert, left, quizzed Filgo, who is a predoctoral fellow in Fenton's group, on details of his research. (Photo courtesy of Steve McCaw)



Dixon, left, learned about the approach Quist took in studying the effects of perfluorooctanoic acid on liver function. Quist's abstract won the SOT 2015 Roger O. McClellan Student Award. (Photo courtesy of Steve McCaw)



Tucker, right, enlightened Yitang Yan, Ph.D., of the NTP Molecular Pathogenesis Group, on her research as a predoctoral fellow in Fenton's Reproductive Endocrinology Group. (Photo courtesy of Steve McCaw)

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National Institute of
Environmental Health Sciences

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