National Institute of Environmental Health Sciences

Environmental Factor

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March 2014

NIEHS Spotlight

World Health Organization and NIEHS launch new collaboration

On Feb. 20, Maria Neira, M.D., helped launch the NIEHS-WHO partnership for promoting public health — in the Americas and worldwide.

Birnbaum highlights human health effects at Gulf oil spill conference

NIEHS participants at Gulf conference review public health findings to date and discuss improving preparedness for future events.

New approaches shape latest council meeting

Following up on changes suggested last September, the council meeting Feb. 19-20 provided more time for council discussion and input to NIEHS planning.

Birnbaum discusses science and funding at talks in UK

NIEHS and NTP Director Linda Birnbaum, Ph.D., was the featured speaker Feb. 12 at the Brunel University London Institute for the Environment Public Lecture.

NIEHS celebrates African American History Month and Bahamian civil rights

On Feb. 7, Crystal deGregory, Ph.D., engaged NIEHS with fascinating stories of the American and Bahamian civil rights struggles.

Science Notebook

Meeting on mammalian transgenerational inheritance fosters collaboration

The NIEHS Division of Extramural Research and Training hosted the Transgenerational Inheritance in Mammals after Environmental Exposure grantees meeting Feb. 12-13.

NIEHS study offers insight into why cancer incidence increases with age Video

Researchers at NIEHS demonstrate that sites of age-associated DNA methylation are disproportionately methylated in a variety of cancers.

Council briefed on Parkinson's premotor symptoms research

Research into the clinical implications of premotor symptoms in Parkinson's disease can lead to better understanding of its causes and early disease processes.

NIEHS-funded scientists say more chemicals linked to neurodevelopmental disorders

In a paper published in Lancet Feb. 20, NIEHS-funded scientists report on the neurotoxicity of industrial chemicals and the vulnerability of the developing brain.

NIEHS Spotlight

NIEHS researcher wins grant to study IGF1 receptor and hippocampal plasticity

The International Rett Syndrome Foundation has announced an award to NIEHS neurobiologist Serena Dudek, Ph.D., a 2-year, $98,000 grant that began in January.

Society of Toxicology conference brings toxicology community together

NIEHS and SOT will sign a memorandum of understanding during the 53rd annual meeting of SOT March 23-27 at the Phoenix Convention Center.

NTP presentations highlight new technologies to protect human health

NIEHS and NTP scientists pursue alternatives to animal testing for toxicity assessments, at January FutureTox II conference, held at UNC, Chapel Hill.

Researchers report decline in some phthalate levels following federal ban

In new study funded in part by NIEHS, researchers found that Americans are being exposed to lower levels of some phthalates banned from children's products.

Conference highlights the known and unknown in fracking debate

Pennsylvania conference presents speakers from academia, government, industry, and the public to explore knowledge of health effects from hydraulic fracturing.

Science Notebook

Research on dopamine and Parkinson's disease illustrates value of exposome studies

Alteration of dopamine storage, which can be affected by exposure to PCBs and certain pesticides, may contribute to Parkinson's disease.

Study finds a new marker for assessing heart inflammation

NIEHS grantee Tomás Guilarte, Ph.D., found that a widely-used biomarker for diagnosing brain injury can also help determine the severity of myocarditis.

NIEHS-funded research shows link between DDT and Alzheimer's disease Audio

A study published Jan. 27 in JAMA Neurology investigates association between exposure to DDT and genetic susceptibility to Alzheimer's disease.

Genetic variation may explain PCB-resistance in Atlantic killifish

SRP-funded researchers find that New Bedford Harbor killifish show evidence of adaptation to the harbor's PCB-contaminated sediments.

New approaches in mustard gas exposure treatment

As part of an ongoing lecture series highlighting the broad range of research by its grantees, NIEHS hosted a talk Feb. 6 by pediatric pulmonologist Carl White, M.D.

NIEHS Spotlight

UNC SRP trainee develops chemical risk assessment interface

Video

Graduate student Andy Shapiro presents webinars on Health Assessment Workplace Collaborative, an online tool he created to support chemical risk assessments.

Peddada honored by Indian statistical society

This winter, NIEHS biostatistican Shyamal Peddada, Ph.D., was presented a prestigious award by the Indian Society of Agricultural Statistics.

SRP grantee receives prestigious Brodie Award for contributions to drug metabolism research

Among his many pursuits, long-time NIEHS grantee Bruce Hammock is recognized for exceptional research and collaboration.

Inside the Institute

NIEHS awards ceremony honors 2013 achievements

The Feb. 11 ceremony recognized unsung heroes, teams, and individuals for their excellence in a variety of endeavors.

Science Notebook

NIEHS study on genome stability highlighted in Genetics

Using a novel assay to study chromosome gain, the researchers described mechanisms that may be employed by cancer cells or pathogenic fungi on the path to drug resistance.

PEPH webinar highlights alternative testing methods

Video

The NIEHS Partnerships for Environmental Public Health webinar Jan. 23 explored the agency's commitment to develop, apply, and validate cutting-edge scientific methods.

This month in EHP

The March issue of Environmental Health Perspectives focuses on health impacts of feminine hygiene products and personal lubricants, and the NTP Nonneoplastic Lesion Atlas.

Distinguished Lecture Series to feature talk by Melissa Moore

Video

The next NIEHS Distinguished Lecture of 2014 will be presented by Melissa Moore, Ph.D., at 11:00 a.m. March 11 in Rodbell Auditorium, hosted by Karen Adelman, Ph.D.

RTI to host NIH metabolomics symposium March 7

RTI International will host the second NIH Eastern Regional Comprehensive Metabolomics Resource Core Symposium March 7 in RTP.

Calendar of Upcoming Events

- **March 3-4**, in Rodbell Auditorium. 8:30 a.m.-5:00 p.m. — Superfund Research Program Arsenic Workshop
- **March 3 (offsite event)**, in the French Family Science Center at Duke University, 11:30 a.m.-12:30 p.m. — Computational Biology Seminar by Bing Ren, Ph.D., on "Long-range Control of Gene Expression — a 3D Perspective"
- **March 4 (offsite event)**, in Auditorium Room 2104 of the Toxicology Building on the Centennial Campus at North Carolina State University, 4:00-5:00 p.m. — Environmental and Molecular Toxicology Program Seminar on "GLIS Transcription Factors: Mechanism of Action and Roles in Development and Disease," by Anton Jetten, Ph.D.
- **March 5**, in Rodbell A, 1:00-2:00 p.m. — Seminar by Richard Peterson, Ph.D., "The Beat Goes on: Dioxin and Disrupted Heart Development"
- **March 7 (offsite event)**, in the Searle Center Lecture Hall at Duke University, 8:30 a.m.-3:00 p.m. — Integrated Toxicology and Environmental Health Program Spring Symposium
- **March 7 (offsite event)**, in Dreyfus Auditorium at RTI International, 8:30 a.m.-5:00 p.m. — NIH Eastern Regional Comprehensive Metabolomics Resource Core Symposium, registration required
- **March 8**, in Rodbell Auditorium, 8:00 a.m.-2:00 p.m. — Triangle Consortium for Reproductive Biology Symposium
- **March 11**, in Rodbell Auditorium, 11:00 a.m.-noon — Distinguished Lecture featuring Melissa Moore, Ph.D., exploring "Assembly and Dynamics of Uber Complex RNPs."
- **March 12**, in Keystone 2164/2166, 9:00 a.m.-5:00 p.m. — NTP Risk Communication Seminar
- **March 23-27 (offsite event)**, at the Phoenix Convention Center — 53rd annual meeting of the Society of Toxicology
- **March 24**, in Rodbell Auditorium, 9:00-10:00 a.m. — NIH Office of Equity Diversity and Inclusion Summit
- **April 1**, in the Executive Conference Room, noon-1:00 p.m. — Receptor Mechanisms Discussion Group Seminar Series presentation on "The Glucocorticoid Receptor: a Role in Mediating Arsenic Toxicity," by Rebecca Fry, Ph.D.
- View More Events: NIEHS Public Calendar

Extramural Research

Extramural papers of the month

- New animal model reveals role of abnormal DNA repair in lupus
- Developmental exposure to BPA increases prostate cancer risk
- Human stem cells reveal gene-environment interaction in Parkinson's disease
- Simulation helps prioritize housing interventions based on health outcomes and costs

Intramural Research

Intramural papers of the month

- SIRT1 plays a vital role in bile acid absorption and homeostasis
- X-ray crystallography reveals previously unknown damage response pathway
- Nicotine has a positive cognitive effect on hippocampal neurons
- Identifying respiratory syncytial virus using gene markers

NIEHS Spotlight

World Health Organization and NIEHS launch new collaboration

By Paula Whitacre

NIEHS and the World Health Organization (WHO) began a new chapter in their decades-long partnership Feb. 20, with the official launch of the NIEHS-WHO Collaborating Centre for Environmental Health Science. NIEHS welcomed Maria Neira, M.D., director of the WHO Public Health and Environment Department, as keynote speaker (see sidebar). The event took place in conjunction with the winter meeting of the National Advisory Environmental Health Sciences Council (see story).

"By joining forces, NIEHS and WHO will help to ensure that cutting edge environmental health science will be translated into effective public health interventions to improve health around the world," said NIEHS and NTP Director Linda Birnbaum, Ph.D.

Building bridges

As a WHO Collaborating Centre, NIEHS joins a network of academic and scientific institutions around the world dedicated to information exchange and technical cooperation.

"Even as the global health community shifts its focus from infectious to non-communicable diseases, the critical role of environmental exposures in adding to the global chronic disease burden is not well appreciated. The Collaborating Centre provides a new and unique platform for NIEHS to address this gap in awareness," said John Balbus, M.D., NIEHS senior advisor for global health and head of the new center.

WHO is the United Nations authority for directing and coordinating global health promotion efforts. It is responsible for providing leadership on health matters, shaping the research agenda, setting norms and standards, articulating evidence-based policy options, providing technical support to countries, and monitoring and assessing health trends.

WHO operates six regional offices, with Collaborating Centres located in more than 80 countries. The member states of WHO comprise most countries of the world, providing an extensive network of health experts and health ministries that the Collaborating Centres can access for research translation and communication. In addition to working directly with WHO, the centers collaborate with each other in formal and informal networks on topics ranging

Whether at breakfast, a roundtable discussion, or the Collaboring Centre launch itself, Neira shared her commitment to preventing adverse enviromental impacts on health. (Photo courtesy of Steve McCaw)

As head of the Collaborating Centre, Balbus will continue to raise awareness of the importance of improving environmental public health worldwide. (Photo courtesy of Steve McCaw)

from adolescent health to zoonoses (diseases and infections that are naturally transmitted between vertebrate animals and humans).

NIEHS focus

The Collaborating Centre at NIEHS will focus on five priorities for research and research translation — children's environmental health, climate change and human health, developmental origins of health and disease, e-waste, and indoor air pollution. "Increased dialogue and understanding is a benefit to being a Collaborating Centre," said Claudia Thompson, Ph.D., a member of the NIEHS Global Environmental Health Program Steering Committee. "The designation also will increase integration across common themes within the Institute."

For example, NIEHS seeks to better understand the link between indoor air pollution and premature deaths, such as through support of intervention studies to investigate realistic alternatives to biomass-burning cookstoves in developing countries. "Having the weight of being a Collaborating Centre, we can see who else has activities in this area around the globe, which should help in coordination and more quickly getting data," Thompson said. "That will help increase dialogue and accelerate findings."

The collaboration

The Collaborating Centre designation culminates three productive decades of partnership, beginning with a cooperative agreement in the early 1980s, facilitated by William Suk, Ph.D., director of the NIEHS Center for Risk and Integrated Sciences and the Superfund Research Program.

As detailed in a 2011 WHO publication, cooperation between the two agencies helped further the International Programme on Chemical Safety and the Environmental Criteria series. With more than 200 peer-reviewed publications, this influential series provides information on a range of environmental health topics to governments.

As a Collaborating Centre, the two organizations will continue to work together to develop training programs, and support and host conferences and workshops related to its five focus areas.

Local global environmental health leaders keep Neira busy in RTP

Neira's schedule included a variety of meetings and events, to provide those with an interest in improving global environmental health the opportunity to meet with her in person.

Breakfast

Neira's day in N.C. began early, with a breakfast presentation at a meeting of the Triangle Global Health Consortium (TGHC). She dispensed with slides and spoke off the cuff about the urgent need to focus on preventive health measures when addressing global health concerns. Neira devoted much of the time to answering TGHC members' questions on topics ranging from economics to the mechanisms of achieving social change.

Midmorning

Next, Neira met with local leaders in global environmental health, including representatives from the University of North Carolina at Chapel Hill Gillings School of Global Public Health, Duke University Nicholas School of the Environment and Global Health Institute, North Carolina State University, the Research Triangle Environmental Health Collaborative, and U.S. Environmental Protection Agency.

NIEHS leadership and lunch

Prior to the afternoon ceremony, Neira spent time with NIEHS leadership, then lunched with members of the NIEHS Global Environmental Health Working Group to discuss the salient features of the collaboration.

Collaborating Centre launch

NIEHS staff, members of the NIEHS Council (see story), and the general public welcomed Neira for a full afternoon devoted to the history of and plans for the Collaborating Centre, before she left for her return flight to Geneva.

NIEHS staff involved with the Collaborating Centre met with staff of WHO and the WHO Pan American Health Organization. Seated, left to right, are Agnes Soares, M.D. (PAHO); Marie-Noël Bruné Drisse, Ph.D. (WHO); Balbus; Birnbaum; Neira; and Luiz Augusto Cassanha Galvao, M.D., (PAHO). Standing, left to right, are Kimberly Gray, Ph.D.; Suk; Kathy Prout (WHO); Claudia Thompson, Ph.D.; Michelle Heacock, Ph.D.; Bono Sen, Ph.D.; Jerry Heindel, Ph.D.; Stephanie London, M.D., Dr.P.H.; and Kimberly Thigpen Tart, J.D. (Photo courtesy of Steve McCaw)

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

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Birnbaum highlights human health effects at Gulf oil spill conference

By Kelly Lenox

NIEHS and NTP Director Linda Birnbaum, Ph.D., led the Institute's delegation to the 2014 Gulf of Mexico Oil Spill and Ecosystem Science Conference Jan. 26-29 in Mobile, Ala.

Opening the Jan. 28 session on "Public Health, Ecology, and Society in the Context of Resilience," Birnbaum distinguished between information collected to guide immediate response efforts, and research needed to address longer-term questions.

"Review of the available literature and health information indicated a clear need for prospective research to understand the health effects to workers, the community, and especially, to sensitive populations," she said.

The session, whose chairs included Dale Sandler, Ph.D., head of the NIEHS Epidemiology Branch, and Symma Finn, Ph.D., health scientist administrator for the Division of Extramural Research and Training Population Health Branch, was the only one during the four-day conference to focus on human health impacts. Other conference topics included fisheries, coastal ecosystems, physical processes, future ecosystem monitoring, oil transport, dispersants, education, socioeconomics, and data management.

"The GuLF STUDY is a tremendous resource for longitudinal data on workers, who are also community members, with the greatest potential for exposure to crude oil, dispersants, and other conditions present during the response efforts," Birnbaum said, addressing the conference in Mobile, Ala.

NIEHS participants focus on public health

Speakers in the public health session included Sandler, who presented "Factors Associated with Current Chemical Exposures in Gulf Residents," and Richard Kwok, Ph.D., staff scientist in the NIEHS Chronic Disease Epidemiology Group, who discussed "Mental Health Symptoms Among GuLF STUDY Participants Involved in the Deepwater Horizon Oil Spill Clean-up."

NIEHS activity was rounded out by two presentations in the associated poster session. NIEHS Senior Medical Advisor Aubrey Miller, M.D., shared an exhibit on disaster health research, and Joseph (Chip) Hughes, director of the NIEHS Worker Education and Training Program (WETP), addressed the spill's mental health consequences.

Assessing mental health among clean-up workers

NIEHS researchers shared some preliminary indications from the GuLF STUDY (see sidebar) — a longitudinal, or long-term, study of nearly 33,000 clean-up workers. Initiated in June 2010, the GuLF STUDY was designed to be a 10-year project.

Because there is a prevailing concern over anxiety and depression among residents of communities damaged by the spill, as a first step in the study, researchers started assessing mental health concerns. Preliminary data indicates that the prevalence of depression and anxiety may be somewhat higher among workers directly involved in clean-up operations than among the general public.

Sandler is head of the NIEHS Chronic Disease Epidemiology Group, which oversees the GuLF STUDY and other large prospective cohort studies looking at the impact of environmental and lifestyle exposures on population health.

Good news on contaminants in blood

Researchers also measured concentrations of heavy metals and certain volatile organic compounds (VOCs) in the blood of study participants. "For the majority of our study participants, we found that levels of metals and VOCs in blood were similar to those levels in the general U.S. population," Sandler said. "This is good news."

Birnbaum noted that WETP trained nearly 150,000 responders in the early days of the spill response, hoping to minimize health risks to clean-up workers. WETP continues its involvement in research and training among responders and health care professionals.

Kwok is co-lead on the GuLF STUDY, which is conducting research on the health of individuals involved in the oil spill clean-up efforts, due to their greater potential for exposure to oil and dispersants.

Lessons learned improve disaster research preparedness

The Deepwater Horizon tragedy highlighted the need for well-designed research in anticipation of, during, and after an emergency, Birnbaum noted. "Previous disasters have clearly underscored the need for timely human health research to help answer pressing questions and concerns," she said. For example, to gather baseline and early impact data, authorities must be able to rapidly mobilize researchers and efficiently authorize research funding.

NIEHS GuLF STUDY tracks health of clean-up workers

Kwok is scheduled to provide an overview of the GuLF STUDY at a Mar. 20 Duke Global Health Exchange lecture.

- Largest-ever prospective study of oil spill clean-up workers, involving nearly 33,000 adults involved in oil spill clean-up or support.
  - Enrolled March 2011 to March 2013
- Baseline telephone interview on jobs, symptoms, health, lifestyle, and socioeconomic factors.
- In-home clinical assessment and biospecimen collection — 11,210 workers and residents of the Gulf states.
  - Now developing a job-exposure matrix for exposure assessment.
  - Unique platform to study a geographically diverse population impacted by the oil spill and other environmental contaminants.
- Next phase:
  - Telephone interview every 2-3 years.
  - Subgroup with repeated mental health and resiliency assessments.
  - Linkage to vital records and cancer registries.
  - More comprehensive clinical exams, in Alabama and Louisiana, of about 4,000 participants, to assess neurobehavioral, respiratory, renal, and mental health effects.

Recognizing this concern, NIEHS developed the new NIH Disaster Research Response Project, which was the subject of Miller's poster. The project's goals focus on data collection tools and protocols, the creation of networks of experts trained as research responders, and integration of the effort into federal response plans for future disasters.

In closing, Birnbaum said, "The combined efforts of federal, academic, and community partners continue to serve as a vital platform for future research, demonstrating a productive and coherent strategy to combine multidisciplinary groups and community-based research activities in response to a disaster."

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New approaches shape latest council meeting

By Ernie Hood

The National Advisory Environmental Health Sciences Council held its 141st meeting Feb. 19-20, highlighting new agenda elements added in response to the council's September 2013 meeting. That gathering included a mini-retreat, during which council members and NIEHS leaders assessed their mutual needs.

Accordingly, this meeting included just one scientific lecture (see related article), fewer formal presentations, more council discussion time, and efforts to elicit council's consultation and advice earlier in the process of formulating new programs.

Collman welcomed a new DERT program administrator to the division. Neuroscientist Jon Hollander, PhD., a former staff scientist at the Scripps Research Institute in Jupiter, Fla., joined the Genes, Environment, and Health Branch, assuming responsibilities with the Parkinson's disease and neurodevelopment portfolios. (Photo courtesy of Steve McCaw)

Council input sought in grant selection criteria

As part of her usual report to the council, Gwen Collman, Ph.D., director of the NIEHS Division of Extramural Research and Training (DERT), included time for council discussion and advice on a proposed new approach to selecting grants that are past the so-called pay line, a percentile-based cutoff point for funding grant awards.

The panel engaged in a robust discussion of the many issues involved. Council member Norbert Kaminski, Ph.D., of Michigan State University, was concerned about setting a conservative pay line. "I could see the pay line continuing to drift downward as money becomes more and more scarce," he said.

Several panelists expressed a desire to see grant applications themselves rather than just the summary statements prepared by staffers. "Can we see something that speaks from the heart of the investigator, so that we're not looking through the glass darkly all the time?" asked Kim Boekelheide, M.D., Ph.D., from Brown University.

Collman noted that perhaps a balance could be struck so that council members can see certain parts of grant applications, but not entire applications, which could give the appearance of circumventing the peer review process.

Along with her usual discussion of legislative activities, science advances, meetings, events, and NIEHS and NTP awards and recognitions, Birnbaum briefed council members on the NIH Disaster Research Response Initiative (DR2). DR2 is a pilot project being led by NIEHS and supported by the National Library of Medicine, aimed at developing ready-to-go research data collection tools and a network of trained research responders. (Photo courtesy of Steve McCaw)

"We have a budget!"

So NIEHS and NTP Director Linda Birnbaum, Ph.D., happily reported to the council, and for the first time in many council meetings over the last few years, thorny budget issues did not dominate. Certainty and stability are welcome trends, but Birnbaum provided an important reminder. "What we have gotten at NIH is about two-thirds restoration of the cuts we had seen due to across-the-board rescission [contract changes] and sequestration reduction," she said.

"The really good news is that we actually have an appropriation," said NIH Principal Deputy Director Lawrence Tabak, D.D.S., Ph.D., who updated the council on current NIH initiatives. "But the not-so-good news is that if you look at our appropriation indexed to 1998 dollars, effectively NIH has become un-doubled in terms of our buying power," he added.

Tabak also updated the council on NIH activities including big data programs, biomedical workforce and diversity initiatives, and challenges in supporting the best science, for example in peer review.

Council member Elizabeth Yeampierre, J.D., executive director of UPROSE, Brooklyn, N.Y., said she was excited about the Disaster Research Response initiative, citing the difficulty presented by a lack of baseline data in the wake of disasters such as Hurricane Sandy. (Photo courtesy of Steve McCaw)

Training discussion

In the spirit of involving the council earlier in the decision-making process, DERT staffers Michael Humble, Ph.D., Carol Shreffler, Ph.D., and Christie Drew, Ph.D., presented the board with both an update on the DERT training program and an opportunity for substantial discussion of current issues and potential directions.

Among several discussion topics, the council focused mainly on determining a healthy balance between institutional T32 training programs and individual fellowships. In April, NIEHS will begin offering NIH F31 Individual Predoctoral Fellowships to graduate students. They will be funded from the same pool of resources as T32 programs.

Tabak described an ongoing series of NIH activities designed to enhance scientific reproducibility and replication. "We need everybody to join together to help overcome what has become an increasingly troublesome set of issues," he said. "But what NIH does alone isn't going to be sufficient, and that's why I used this opportunity to address your council," he added, citing the fact that all council members were likely editors or on the editorial boards of scientific journals and in a position to influence reproducibility criteria. (Photo courtesy of Steve McCaw)

"The fundamental question is, what benefits are there to NIEHS to reaching the goals of the strategic plan by moving money out of the T32s and into F31 programs?" asked David Eaton, Ph.D., of the University of Washington. Humble noted that the change would enhance the flexibility of the training program.

Concepts approved

The council also voted unanimously to approve concepts involving mitochondria, energetics, epigenetics, environment, and DNA damage response (commonly referred to as MEEED), environmental health disparities research, and new training initiatives for the Worker Education and Training Program.

The next council meeting is scheduled for May 13-14.

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

Council member Mary Lee, M.D., of the University of Massachusetts Medical Center, right, asked Tabak about the lack of a gold standard in NIH funding deliberations. He replied that despite myriad analytic efforts, "The gold standard remains expert opinion." (Photo courtesy of Steve McCaw)

From right to left, council members Linda McCauley, Ph.D., R.N., of Emory University, Randall Kramer, Ph.D., of Duke University, and Kaminski paid close attention to the meeting's proceedings. (Photo courtesy of Steve McCaw)

Discussing the proposed environmental health disparities research concept, council member Lisa Conti, D.V.M., of the Florida Department of Agriculture and Consumer Services, noted the importance of partnering with state agencies that are anxious to share their considerable databases with researchers. (Photo courtesy of Steve McCaw)

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Birnbaum discusses science and funding at talks in UK

By Eddy Ball

NIEHS and NTP Director Linda Birnbaum, Ph.D., was the featured speaker Feb. 12 at the Brunel University Institute for the Environment (IfE) Public Lecture in London.

Birnbaum's talk, "Environmental Exposures Acting Like Uncontrolled Medicine," was hosted by IfE head Susan Jobling, Ph.D. IfE is recognized internationally for its research in environmental science, and it has strong international links with pharmaceutical industries, water companies, and government authorities charged with protecting the environment and health of humans and wildlife.

The following day, Birnbaum joined Jobling and other environmental scientists for a Developmental Origins of Health and Disease (DOHaD) roundtable. Birnbaum's remarks focused on a disturbing trend in funding for scientific research and development in the U.S. and Canada, which declined as much as 5 percent from 2012 to 2013, while funding in China increased by 15 percent.

One theme throughout Birnbaum's talk was the power of knowledge to inform prevention. "The choices we make regarding the foods we eat, exercise, and the chemicals we are exposed to will make a difference in our wellness," she said in conclusion. (Photo courtesy of Brunel University)

An eye-opening analogy

Birnbaum opened her talk by acknowledging the remarkable advances in medicine during the past 40 years. "Drugs have been developed that can raise or lower our blood pressure, mimic our endogenous hormones, block receptor binding, upregulate or downregulate biological pathways, and stimulate growth," she told the audience.

"Unfortunately, environmental chemicals can also act like drugs," Birnbaum said, as her focus shifted from the wonders of medicine to the potentially harmful effects of the thousands of untested chemicals in the environment. "The WHO [World Health Organization] estimates that approximately 25 percent of the overall global burden of disease is attributable to environmental factors."

As medicine's success at combating infectious diseases among children and young adults has been widely applauded, Birnbaum said that largely silent epidemics of chronic, and often complex, noncommunicable diseases (NCDs) have increased dramatically worldwide. The environmental link to infectious disease is clear, and the direct effects of polluted water and air are becoming more apparent. But, she added, recent research also suggests that environmental exposures also play a more subtle, but potentially significant role in predisposing people to the major NCDs, such as diabetes, cardiovascular disease, reproductive anomalies, and even cancers.

Established in 1966, Brunel University takes pride in its Institute for the Environment, whose research revealing the link between chemicals in rivers and reproductive health won a 2011 Queen's Anniversary Prize for Higher and Further Education.

Linking cause and effect across the decades of life

Pointing to what she called the new science, Birnbaum described the concepts of exposure to mixtures, nonmonotonic dose response, and epigenetic modification. These processes may set the stage *in utero*, in infancy, and during other windows of susceptibility during development, for diseases that may not manifest until decades later or in succeeding generations.

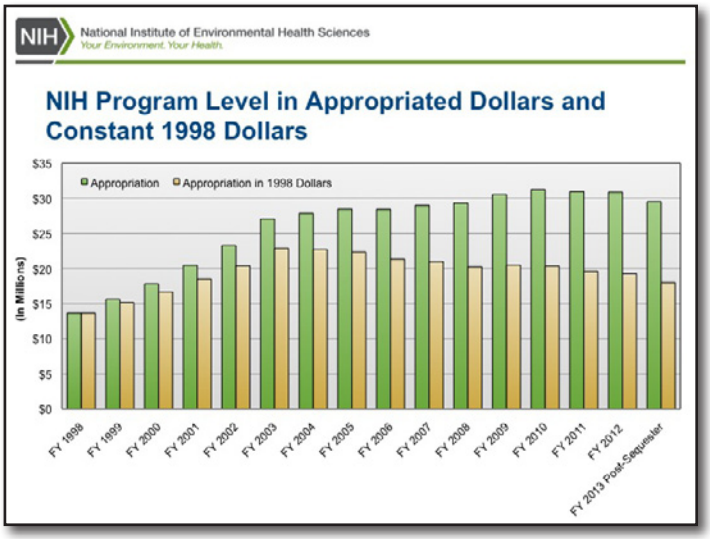
Instead of causing disease by overwhelming the body at high doses, some chemicals can act like hormones and drugs to disrupt development and change gene expression at very low doses. In combination, chemicals and other environmental triggers, such as stress, can have a far greater effect than they do in isolation.

This slide from Birnbaum's public lecture outlines several principles of the new science. (Slide courtesy of Linda Birnbaum)

NIEHS and NTP programs offer hope for the future

Birnbaum presented findings from several recent studies that support the hypotheses of the new science, before turning to proactive efforts by NIEHS and NTP scientists to prevent exposures in the first place. She pointed to NIEHS and NTP support for the principles of green chemistry and safe-by-design engineering of new products that do not persist in the environment. She then moved to the final part of her talk, which was devoted to the emerging paradigm of predictive toxicology through efforts such as the Tox21 consortium (see related story).

With an estimated 80,000 chemicals in the environment, Birnbaum explained, it's impossible to test even a fraction with conventional methods using rodent or other mammalian models. A much more effective and economically feasible approach involves the development of alternative testing, using lower-order organisms, such as zebrafish, worms, and flies, along with rapid throughput biochemical and cell-based *in vitro* assays, and computational analysis of the biochemical pathways that lead to disease.



Despite the multiple benefits of NIH research to improving health and promoting economic viability, Birnbaum told DOHaD roundtable participants, appropriations have not kept pace with need. Funding adjusted for inflation, shown in yellow, has increased very little since fiscal year (FY) 1998 and even declined since its peak in FY 2003. (Slide courtesy of Linda Birnbaum)

Enhancing the ability to predict toxicity can help manufacturers, regulators, and individuals make better choices about environmental public health, Birnbaum concluded.

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NIEHS celebrates African American History Month and Bahamian civil rights

By Kimberly Cannady

In honor of African American History Month, NIEHS hosted a series of activities Feb. 7 to celebrate the achievements of past civil rights activists and provide mentoring and networking opportunities. The theme for this year, Civil Rights in America, coincides with the 50th anniversary of the Civil Rights Act of 1964.

The keynote speaker for the event, Crystal deGregory, Ph.D., is founder and executive editor of HBCUstory. A native of Freeport in the Bahamas, deGregory fused this year's theme with her country's civil rights movement, giving an engaging presentation titled "Herstory: Civil Rights (and Wrongs) at Home and Abroad."

She began her presentation with pictures of famous Bahamians, such as Sidney Poitier, Roxie Roker, Esther Rolle, and Bert Williams, highlighting the importance of these actors and musicians to American culture. Not one to shy away from her Bahamian pride, deGregory included herself in the list, as a nationally known advocate for African American culture advancement and awareness.

With her high-energy presentation about the Bahamian Revolution, deGregory commandeered the attention of the audience. (Photo courtesy of Steve McCaw)

The quiet revolution of the Bahamas

Demonstrating her talent as a dynamic storyteller, deGregory's interwoven stories illustrated how the civil rights movement in America influenced the revolution in the Bahamas during the 1950s and 1960s.

Sir Randol Fawkes, a famous Bahamian civil rights activist, figured prominently in many anecdotes. Fawkes followed the American civil rights movement, especially the actions of Martin Luther King Jr., to help shape the Bahamian revolution. In 1958, Fawkes led the Taxi Cab Union strike, the Bahamian equivalent of America's Montgomery bus boycott in 1955. Fawkes urged a nonviolent protest, a concept that resonated throughout the civil rights movement.

King wrote to Fawkes after visiting the Bahamas in 1958. In the excerpt deGregory shared, King highlighted the immense role Fawkes had in the Bahamian revolution. "I will long remember the expression of genuine goodwill and moral support on the part of the people of your community," wrote King. "Please allow me to express my personal appreciation to you for your determined courage and dedication to the cause of freedom and human dignity. I am sure your name will live long in the annals of your nation's history for your willingness to suffer and sacrifice for a cause that you know is right."

Welcoming remarks from Joellen Austin, NIEHS associate director for management, included a brief introduction of the origins of the African American History Month celebration, and touched on key events of its theme, Civil Rights in America. (Photo courtesy of Steve McCaw)

Majority rule achieved

In 1967, the determination of the Bahamians paid off when a majority of black representatives were voted into the house of assembly. “There was a triumphant resolve of majority rule,” said deGregory. In addition, the Bahamas elected Sir Linden Oscar Pindling as its first black premier in 1967 and prime minister in 1969. He ruled for 25 years.

Summarizing the election day moment, deGregory said, “It was one, not just for black Bahamians, but also for black Americans as they traveled to the Caribbean to be a part of the new spirit.” She concluded her remarkable presentation by declaring, “The civil rights movement in the Bahamas did not happen by chance or in isolation. All across the African diaspora [scattered population], there were changes in the people, the nation, and in the world.”

After the lecture, deGregory participated in a meet and greet, as well as speed mentoring networking sessions. The intimate setting fostered dialogues between strangers, enabling participants to learn about events and programs at NIEHS and in the wider community. It was an appropriate way to end a day focused on celebrating civil rights in America, as it highlighted the eagerness of the community to come together and promote advancement.

Charletta Fowler was among the audience members who enthusiastically enjoyed deGregory’s stories of Bahamian and African American culture. (Photo courtesy of Steve McCaw)

(Kimberly Cannady, Ph.D., is an Intramural Research Training Award (IRTA) fellow in the NIEHS Chromatin and Gene Expression Group.)

Members of the NIEHS Diversity Council welcomed deGregory to NIEHS. From left, Brad Collins; Veronica Godfrey Robinson; Ron Herbert, D.V.M., Ph.D.; deGregory; Victoria Gross, NIH Black Employment Program Manager, NIH Office of Equal Opportunity and Diversity Management; and Austin. (Photo courtesy of Steve McCaw)

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NIEHS researcher wins grant to study IGF1 receptor and hippocampal plasticity

By Kelly Lenox

The International Rett Syndrome Foundation, in January, awarded a 2-year, $98,000 grant to NIEHS researcher Serena Dudek, Ph.D., to study the role of insulin-like growth factor 1 (IGF-1) receptor in hippocampal CA2 plasticity and function.

IGF-1 has shown promise for treatment of Rett syndrome (RTT), a serious and poorly understood neurological disorder (see sidebar). Dudek, noting that the primary receptor for this growth factor is highly expressed in the CA2 region of the hippocampus, proposes that novel insights into the nature of RTT may be gained by studying the effects of IGF-1 signaling in CA2 pyramidal neurons.

Dudek heads the NIEHS Synaptic and Developmental Plasticity Group in the Laboratory of Neurobiology. By studying factors affecting development and function of the brain's synapses, the group pursues deeper understanding of how environmental factors affect the circuitry of the brain. Her group is one of a very few labs, worldwide, investigating synaptic plasticity in the CA2 area, and one of a handful at NIEHS successfully applying for outside support to pursue its studies (see text box).

"We're excited at the possibility that the grant will raise the visibility of CA2 research among those interested in autism and other developmental disorders. I'm a strong believer in basic research and am excited about the opportunity to research Rett syndrome, which we wouldn't have without this grant."

Unique opportunity

Dudek's lab previously found that, although the hippocampus is known for its synaptic plasticity, the CA2 area, in particular, is not very plastic. In fact, the CA2 differs from other hippocampal areas in a number of structural, molecular, and physiological ways. One of those differences is that the IGF-1 receptor is more highly expressed in CA2 than almost anywhere else in the brain.

"Since we have expertise in CA2 physiology, where the receptor is highest, it seemed like an opportunity not to pass up," Dudek said. "Our work will provide insight into how IGF-1, which is currently undergoing clinical trials, is acting on CA2 neuron function." The results of the study may shed light on the outcome of the clinical trials and be crucial for developing the next generation of drugs.

Rett Syndrome (RTT)

RTT is a severe neurological disorder caused by a mutation in the MECP2 gene. Because the gene is located on the X chromosome, RTT most often affects girls.

Referred to as a housekeeping gene, the MECP2 gene is responsible for telling downstream genes when to shut off. Mutations may cause certain regions of the brain to either remain developmentally immature or to be flooded with an overproduction of proteins and enzymes. The type of mutation and the number of cells affected appear to determine when normal development will cease.

MECP2 mutations are also involved in other disorders, including autism, mental retardation, learning disorders, schizophrenia, and bipolar disorder.

Persons with RTT may have varying degrees of disability. It affects brain functions responsible for cognitive, sensory, emotional, motor, and autonomic function. More information on RTT is available from the National Institute of Neurological Disorders and Stroke.

RTT and the hippocampus

RTT is associated with a mutation in the MeCP2 gene, located on the X chromosome. Other researchers have shown that mice bred to be deficient in the MeCP2 gene have smaller CA2 neurons. Research funded by this grant will determine whether, when treated with IGF-1, the impact on the anatomy or physiology of CA2 pyramidal neurons is different from the impact on other hippocampal or cortical neurons, in both wild type and MeCP2-mutant mice.

Dudek's team previously found that synaptic potentiation in CA2 could be pharmacologically induced with agents, including caffeine and the social neuropeptides vasopressin and oxytocin, at concentrations that had little effect in other regions of the hippocampus. That finding, combined with other studies implicating the hippocampus in social behavior in rodents, led her team to hypothesize that CA2 is the social module of the hippocampus. The new study is designed to determine whether CA2 is implicated as a critical module of cognitive processes affected by RTT.

Growing ranks of NIEHS awardees

According to William Schrader, Ph.D., deputy scientific director of the NIEHS Division of Intramural Research, about one NIEHS scientist a year is awarded a grant from an external source, though many more apply. As Schrader explained, "There are not a lot of grants for which NIEHS intramural scientists are eligible to apply. Dudek is a good example of an investigator who found that her work was directly on point with a grant opportunity and took advantage of it."

NIH is working to increase successful applications among staff of all the institutes, according to Darryl Zeldin, NIEHS scientific director (SD) and head of the Environmental Cardiopulmonary Disease Group in the Laboratory of Respiratory Biology. "Michael Gottesman [M.D.] in Bethesda, the deputy director for all intramural research programs, is compiling, for all SDs, a list of organizations whose funds NIH is eligible to apply for, and where we have been successful, so that SDs can encourage scientists to apply," said Zeldin.

In addition to easing the burden of tight funding, such grants raise visibility for the work of NIEHS scientists. "Dudek's grant is a great example of a small organization that doesn't give a lot of money out, but if you get a competitive proposal from a top researcher like Serena you can be successful," Zeldin continued. "All of these smaller organizations do publicity around which researchers get grant money and what they're studying, so it's very good visibility for NIEHS."

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Society of Toxicology conference brings toxicology community together

By Robin Mackar

As a prelude to the hundreds of science talks that will be given during this year's Society of Toxicology (SOT) conference, NIEHS and SOT will sign a memorandum of understanding (MOU) during the 53rd annual meeting of SOT, March 23-27, at the Phoenix Convention Center.

The signing will occur Sunday afternoon, March 23. Shortly after NIEHS and NTP Director Linda Birnbaum, Ph.D., talks to undergraduates about career opportunities in toxicology, she will meet up with SOT president Lois Lehman-McKeeman, Ph.D., and SOT council members to officially sign the MOU.

Afterwards, NIEHS and NTP staff will join conference proceedings, leading or attending the abundance of science talks, poster sessions, and awards that will occur at the meeting.

Program highlights for NIEHS and NTP

The cornerstone for the upcoming conference will be exhibit booth 1129, which will provide visitors with all the information they want to know about NIEHS and NTP.

Some of the highlighted events that NIEHS will participate in at SOT include:

- A Conversation with the Director of NIEHS, Monday, March 24, 1:30-2:30 p.m. This special symposium will provide an informal venue for meeting attendees to have a candid and open discussion with the director concerning the direction and scientific priorities of NIEHS, as well as funding opportunities.

- Informational Session on Leadership in Science: Skills and Styles, Wednesday, March 26, 4:30 p.m. This session will include presentations by Birnbaum and other key leaders from government, academia, industry, and consulting. The speakers will discuss some of the core skills and styles required to be an effective leader.

Research funding information

Program and review staff from the NIEHS Division of Extramural Research and Training will be available in the research funding information room, Room 127A, Monday, March 24, and Tuesday, March 25, for individual conversations with attendees interested in grant opportunities. New investigators are encouraged to stop by.

A brown bag luncheon, focusing on strategies for submitting successful grants, will be held Tuesday, March 25, at noon. Panelists will talk about the grant submission process, provide advice on how to submit a potentially successful grant, and offer tips about how to make a submission stand out. Additionally, SOT will be hosting webinar discussions about funding opportunities all day on Wednesday, March 26, allowing participants to hear from program staff unable to attend SOT.

Exhibitor Sessions

Two exhibitor sessions are planned for this year's SOT.

On Monday, March 24, from 10:30-11:30 a.m., NTP will share information about its newest resource, the NTP Nonneoplastic Lesion Atlas. The atlas is a searchable, Web-based tool containing thousands of high quality images and guidelines for diagnosis of nonneoplastic lesions in rodent models. NTP pathologist Mark Cesta, D.V.M., Ph.D., will also be conducting tutorials on the atlas at the NIEHS exhibit booth on Tuesday and Wednesday morning from 9:00-11:00 a.m.

Also, Allen Dearry, Ph.D., NIEHS Office of Scientific Information Management director, will lead a session on Monday, March 24, from 2:15-3:15 p.m., that will focus on "Advancing Environmental Health Data Sharing and Analysis."

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

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NTP presentations highlight new technologies to protect human health

By Catherine Sprankle

New technologies such as high-throughput and high-content screening generate large amounts of data on potential toxic effects of chemicals. However, making sense of the data and using it to predict the effects of chemicals on human health remain a challenge. More than 20 NIEHS and NTP scientists joined nearly 300 researchers Jan. 16-17 at the University of North Carolina at Chapel Hill Friday Center to address this challenge.

"FutureTox II: *In Vitro* Data and *In Silico* Models for Predictive Toxicology" brought together experts in computational and high-throughput non-animal toxicology methods. The goal of the conference was to consider how these new technologies could lead to faster, cheaper, and more relevant alternatives to animal testing, to assess the potential toxic effects of chemicals.

NIEHS and NTP presenters discuss alternative toxicity data

Plenary sessions focused on biological systems, predictive models, and regulatory integration and communication. Among the presenters in the session on predictive models were NIEHS Deputy Director Richard Woychik, Ph.D., and Scott Auerbach, Ph.D., of the NTP Biomolecular Screening Branch.

Woychik focused on using stem cells derived from outbred mouse populations as a model for identifying variations in toxicity among humans. Auerbach discussed the use of gene expression data, from cells treated with chemicals that have known toxic effects, to predict possible toxic effects of related chemicals that are lacking toxicity data.

NTP Associate Director John Bucher, Ph.D., center, listens to plenary session presentations with other meeting attendees. In addition to those attending in person, about 150 viewed the plenary session presentations via webcast in nine locations in the U.S. and Canada. (Photo courtesy of Ivan Rusyn, M.D., Ph.D., of the University of North Carolina at Chapel Hill)

Alternatives for endocrine disruptor and skin sensitizer identification

NTP scientists presented 10 posters at the Jan. 16 poster session. Of these, five from the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) addressed ongoing projects to develop alternative methods for identifying potential endocrine disruptors and skin sensitizers. Other posters were presented by members of NTP's Biomolecular Screening Branch and Toxicology Branch.

A poster by Nicole Kleinstreuer, Ph.D., contractor for NICEATM, outlined an approach that uses data from the EPA ToxCast research program to identify potential skin sensitizers. "The poster session was well-attended. The research presented on the posters was very timely and relevant to the goals of the meeting and generated some lively discussions." Kleinstreuer commented. "Overall, this was a very informative and productive meeting."

The spacious atrium of the Friday Center was the perfect venue for attendees to view and discuss the poster presentations. (Photo courtesy of the Society of Toxicology)

Strategies for application of new methodologies

Following the plenary and poster sessions, conference participants attended breakout groups to discuss strategies for applying the testing approaches to areas of current interest. The four breakout discussions focused on regulatory toxicology, liver toxicity, cancer, and developmental and reproductive toxicity.

Conference organizers will prepare an article on the outcomes of the meeting, for submission to the Forum section of the journal Toxicological Sciences later this year. Also, conference attendees will be invited to contribute manuscripts on conference topics to a special issue of Reproductive Toxicology.

(Catherine Sprankle is a NICEATM Communications Specialist and works for ILS, the contractor supporting NICEATM.)

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Researchers report decline in some phthalate levels following federal ban

By Bailey Schug

In a new study funded in part by NIEHS, researchers found that Americans are being exposed to lower levels of some phthalates banned from children's products. At the same time, exposure to other forms of these plasticizing chemicals has increased significantly.

In an analysis of data from the Centers for Disease Control and Prevention National Health and Nutrition Examination Survey (NHANES), researchers from University of California, San Francisco (UCSF) analyzed how phthalate exposure has changed over time. The findings, which were published in the January issue of the journal Environmental Health Perspectives, is the first of its kind to examine changes in phthalate exposure over time using a large representative sample of the U.S. population. The researchers examined NHANES data on urinary concentrations of eight different phthalate metabolites from 2001-2010.

Zota has also co-authored NIEHS-funded studies on other endocrine disrupting compounds, including chemicals used as fire retardants during her time at UCSF (see story) and earlier (see story) with colleagues at the Silent Spring Institute (Photo courtesy of Ami Zota)

Phthalates are a group of chemicals used to soften and increase the flexibility of plastic and vinyl, and are used in hundreds of consumer products. They are not chemically bound to products and are, therefore, released into the environment where they may enter the human body by ingestion, inhalation, or dermal absorption. The chemicals have been linked to reproductive anomalies in animal studies, and are associated with premature birth, as well as cognitive and behavioral problems, in human epidemiological studies.

Woodruff's research focuses on the effects of environmental exposures, during windows of susceptibility in gestation and early childhood, on the lifelong health of children. (Photo courtesy of UCSF)

Change in phthalate exposure over time

"We were excited to see that exposure to some of the phthalates that are of public health concern actually went down," said Ami Zota, Sc.D., corresponding author on the study, in a UCSF press release. "Unfortunately, our data also suggest that these are being replaced by other phthalates with potential adverse health effects."

Zota, who was a postdoctoral fellow at UCSF when the study was conducted, is now an assistant professor in the Department of Environmental and Occupational Health at George Washington University.

Like other studies, this one found that nearly all NHANES participants have been exposed to at least one of the eight phthalates that were measured, including ones partially banned under a law that took effect in 2009.

Government and private groups at work to reduce phthalate exposure

As expected, declines were observed in metabolites of those phthalates that have been the focus of regulatory efforts. However, these bans are not entirely responsible for the observed trends. The largest reductions were seen in diethyl phthalate (DEP), a chemical used in fragrances that is neither regulated in the U.S. nor the European Union.

The federal ban is not the only force at work in determining phthalate exposures. Both consumers and industry have also changed their behavior, in response to action by the state of California, and advocacy by such groups as the Campaign for Safe Cosmetics. Since 2004, more than 1,000 companies have agreed to remove certain chemicals from personal care products, and report more clearly what chemicals they are using.

However, the researchers said it is hard to know, for sure, how changes in industry preference and consumer behavior are affecting human exposures, given how little is known about the chemical composition of consumer products.

"Our study shows the power of monitoring exposures to chemicals, so we can identify where we have made progress and where more information is needed," said the study's senior author, Tracey Woodruff, Ph.D., who directs the Program on Reproductive Health and the Environment at UCSF. "It also indicates that actions by government and consumer groups can make a difference in exposures in all Americans."

Citation: Zota AR, Calafat AM, Woodruff TJ. 2014. Temporal trends in phthalate exposures: findings from the National Health and Nutrition Examination Survey, 2001-2010. Environ Health Perspect; doi:10.1289/ehp.1306681 [Online 15 January 2014].

Phthalates in consumer products

According to the study's literature review, phthalate acid esters, also known as phthalates, are the predominant type of plasticizer used around the world. Low molecular weight phthalates, such as DEP, di-*n*-butyl phthalate (DnBP) and di-iso-butyl phthalate (DiBP), are used in personal care products, solvents, adhesives, and medications. High molecular weight phthalates, such as butylbenzyl phthalate (BBzP), di(2-ethylhexyl) phthalate (DEHP), di-iso-nonyl phthalate (DiNP), and di-iso-decyl phthalate (DiDP), are primarily used as plasticizers in polyvinyl chloride (PVC) applications found in building materials, cables and wires, toys, and food packaging.

Six of the phthalates have been banned from use in children's articles, such as toys. Three were permanently banned, and three were subjected, pending further study, to interim restriction in toys that can be placed in a child's mouth. Phthalates banned include BBzP, DnBP and DEHP. According to the research, exposure to these three chemicals decreased, but DEHP levels remained consistently higher in children than adults, with the levels of exposure narrowing with age differences over time.

Unexpectedly, levels of the phthalates that Congress banned, pending further review, increased in the study research period. Levels of di-*n*-octyl phthalate (DnOP) and DiDP increased by 15 to 25 percent, and DiNP levels grew by nearly 150 percent. DiNP has begun to replace DEHP as a plasticizer in the global market. Toxicology studies suggest that DiNP may disrupt androgen signaling and act cumulatively with other phthalates to affect male reproductive endpoints.

(Bailey Schug studies health promotion at Appalachian State University. She is an intern with the NIEHS Office of Communications and Public Liaison.)

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Conference highlights the known and unknown in fracking debate

By Kim Eisler

A day-long forum on what is known — and especially what is not known — about the public health impacts of hydraulic fracturing (HF) attracted a blizzard-weary crowd of 190 people to the University of Pennsylvania's (UP) Perelman School of Medicine. The Feb. 18 symposium was sponsored by the UP Center of Excellence in Environmental Toxicology (CEET), which is funded in part by NIEHS and the Center for Public Health Initiatives, and featured presenters from industry, academia, government, and the community.

CEET director Trevor Penning, Ph.D., professor of pharmacology and of biochemistry and molecular biophysics at the UP Perelman School of Medicine, opened the symposium with an outline of current challenges. The event ended some seven hours later, with an acknowledgment by Aubrey Miller, M.D., NIEHS senior medical advisor, about how much critical data is simply missing in action. "What is as important as what we know, is all that we still don't know," Miller said.

Miller's comments came after a day of presentations and discussions by experts, oil industry figures, Pennsylvania state government representatives, and academic and community group leaders. The presentations focused primarily on the Marcellus Shale activities in northern Pennsylvania counties where the politics and science of fracking have clashed most dramatically, and where several new NIH/NIEHS-funded studies of

health effects, looking at insurance claims data, hospital records, and community perceptions, are taking shape. Additionally, recent research looking at birth outcomes in Colorado was discussed.

Acknowledging deficits in critical baseline measurements of ground, air, and water effects, Miller praised the citizenry that has stepped in, particularly in Pennsylvania's Marcellus Shale region, to create science from the bottom up. (Photo courtesy Steve McCaw)

Communities play a leading role

Penning discussed development of CEET's Environmental Health Sciences Core, which has brought together 16 university programs to engage in health research and community outreach. One success of the working group was connecting the academic community to HF-impacted communities, to ensure research is connected to the people most likely to be affected.

"The community should determinate how to disseminate the findings, and the community should be first to hear the results," Penning continued. "People need to know who is funding the research, and we need to determine whether rapid changes are overwhelming the fabric of communities."

According to Penning, one of the priorities is to develop valid indicators of early ground water contamination. He also called for more research on the chemicals used for HF and flowback waters, more study of the damage done by dirt kicked up by diesel trucks, as well as more information about the health effects of exposure to respirable crystalline silica, a mineral used in great quatities at each HF site.

Data gaps remain

In his summation, Miller observed that the key issue here is what's missing. "What do I tell people they should be concerned about? Do we have an answer to their concerns, and if not, why not?"

"With 52,000 wells, how can we have no data on an enterprise of this magnitude?" Miller asked. "There are studies, there are health surveys, but there is not enough hard data to even tell people what the risks are. There is very little representative exposure data from the air, from the water, and from the ground to judge the health risks to workers or communities. Additionally, we need information on the mixed effects that these exposures may have on animals, on livestock, on birds, and on fish."

According to Miller, this situation calls for a paradigm shift in the way data on a national scale is being collected. "Instead of waiting for someone to bring them the news, government agencies, academic researchers, and communities, including citizen scientists, need to pool together to collect the missing data," he said. "Communities and concerned citizens need to take a proactive part in efforts to understanding exposures in their own environment."

(Kim Eisler is a contract writer with the NIEHS office in Bethesda, Md.)

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UNC SRP trainee develops chemical risk assessment interface

By Sara Mishamandani

Andy Shapiro, a Master of Science in Public Health student at the University of North Carolina at Chapel Hill (UNC), recently presented a series of webinars on the Health Assessment Workplace Collaborative (HAWC), an online workspace designed to simplify the complex process of conducting chemical risk assessments.

Shapiro, right, meets with Rusyn, left, to discuss how to demonstrate the features of HAWC and its value to chemical risk assessors. (Photo courtesy of Ivan Rusyn)

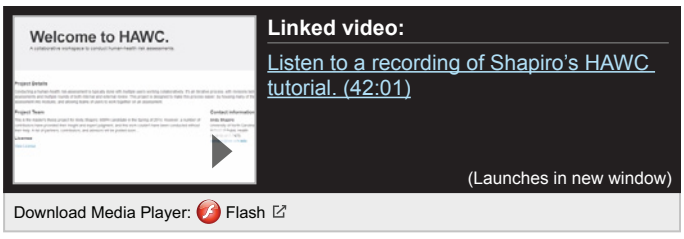
Shapiro developed the content management system under the guidance of NIEHS-funded Superfund Research Program (SRP) grantee Ivan Rusyn, M.D., Ph.D., a professor of environmental sciences and engineering at the UNC Gillings School of Global Public Health.

"HAWC is a Web-based workspace to create, store, share, and display data and analyses conducted in the process of preparing human health assessments of chemicals," said Shapiro. "By creating integrated modules for capturing key steps in the process of conducting an assessment, HAWC is aimed at a variety of potential users and types of human health assessments."

Data sharing and integration

"A number of recent National Research Council committees weighed in on the need for regulatory agencies that conduct human health assessments," said Rusyn. "There was a need to increase transparency of the process, to implement best practices of the systematic review, and to improve data integration and visualization, so that the end users, from risk managers to the general public, would better understand how the decisions are made."

A human health risk assessment typically involves several individuals and organizations working together to review assessments, with multiple rounds of both internal and external review.



HAWC is designed to make this process easier, by integrating, into an online interface, existing information about chemicals, tools to evaluate how the chemicals affect health risk, and current guidance and approaches to assessing risk. The workspace facilitates the risk assessment process, by grouping many of the key components into easy-to-follow modules with multiple user access. HAWC also allows for a more transparent health assessment process, with track changes and version control features.

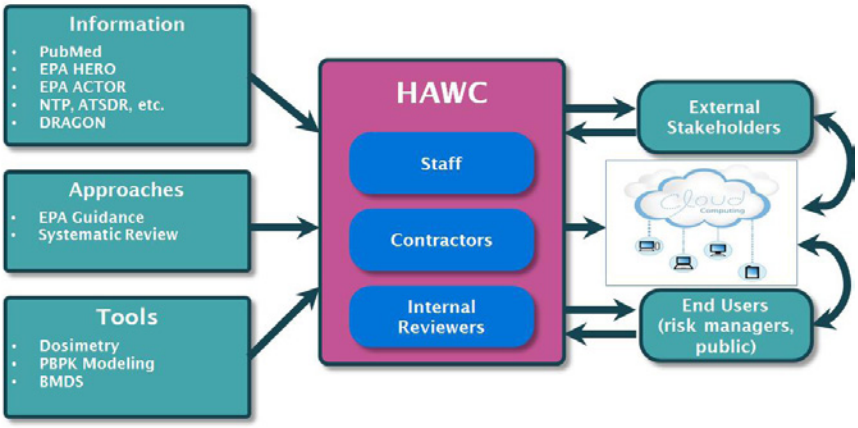
Reaching international stakeholders

In late January, Shapiro presented the first two webinars, including an overview and tutorial on HAWC, to more than 100 callers. Participants called in from a variety of state, federal, and international government agencies, academic institutions, chemical goods manufacturers, and consulting companies.

Two additional webinars were held in February with the International Agency for Research on Cancer, European Food Safety Authority, and Food Standards Agency, which represented international and European interests.

According to Rusyn, the webinars reached several hundred participants and resulted in active sign-ups and use of the website.

"We are making use of the latest technology to move the process into the cloud, so that the transparency and communication goals are met, as well as an attempt to make updates to existing assessments easier in the future," said Shapiro. "This enables stakeholders to engage, participate, and dive into the details."



The webinars explained how HAWC fits into the human health assessment process, and how it facilitates data storage, analysis, and visualization into a pipeline that is easier to review and interpret. Shapiro conducted a live demonstration of several key features of HAWC, including literature search, tagging for inclusion or exclusion, data extraction, and dose-response analysis using the benchmark dose modeling. (Image courtesy of Andy Shapiro)

The project is funded in part by the UNC SRP, with additional funding from the UNC Graduate School, U.S. Environmental Protection Agency (EPA), and National Toxicology Program (NTP).

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

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Peddada honored by Indian statistical society

By Eddy Ball

This winter, NIEHS biostatistician Shyamal Peddada, Ph.D., received a prestigious award from the Indian Society of Agricultural Statistics (ISAS).

During the 67th ISAS annual conference Dec. 18-20, 2013, at Banaras Hindu University in Varanasi, India, Peddada was awarded the 2013 Professor P.V. Sukhatme Gold Medal Award *in absentia* for significant contributions to the field of statistics or agricultural statistics. ISAS recognized Peddada's career-long work in statistical theory and methods, as well as his collaborative research in cell biology, environmental health, fibroid growth in women, the microbiome, and toxicology (see text box).

"This award is a testament to the impressive range of Shyamal's research," said Clarice Weinberg, Ph.D., head of the NIEHS Biostatistics Branch. "It also underscores his valuable contributions to interdisciplinary research in the environmental sciences."

Peddada credits NIEHS with helping his career flourish. "I think that it is a biostatistician's dream job to be working in a data-rich environment such as the one that we have here," he said. (Photo courtesy of Steve McCaw)

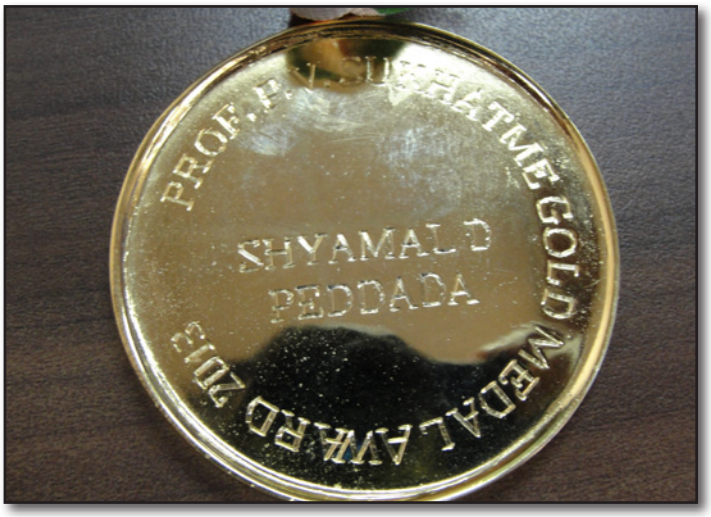
Building on a grand tradition of (bio)statistics

Peddada readily acknowledged the influence that some of the outstanding thinkers in 20th century statistics have had on his own work. He also expressed his gratitude for the intellectually stimulating environment at NIEHS.

"Each award that I've received is special in its own way," Peddada said, "and this one is special because it is named for an eminent statistician, P.V. Sukhatme, who made fundamental contributions to the field of survey sampling, which is widely used in the agricultural sciences, epidemiology, social sciences, and many other areas. Foundations for some commonly-encountered terms, such as stratified sampling, multistage sampling, double sampling, and nonsampling errors, are rooted in Sukhatme's publications in the 1930s to 1950s."

According to Peddada, statisticians, such as Sukhatme, developed a broadly applicable statistical methodology that is central to his own approach to scientific research. Peddada's training with one of the greatest statisticians of the 20th century, C.R. Rao, Ph.D., Sc.D., a fellow of the Royal Society and a member of the National Academy of Sciences, also helped shape his approaches to statistical theory, design of experiments, and the practice of statistics.

"Rao provided the foundations for various aspects of statistical theory and methodology as practiced today," Peddada said. "For example, virtually every textbook on the foundations of statistics contains Rao's fundamental theorems and methods."



Peddada's award is named for Pandurang Vasudeo Sukhatme, Ph.D., D.Sc. (1911-1997), one of the leaders in the establishment of IASRI. In addition to his fundamental contributions to survey sampling, Sukhatme is recognized as a pioneer in the application of statistical methods in studying human nutrition. (Photo courtesy of Shyamal Peddada)

A distinguished career in academia and government

Peddada has received numerous awards for his professional accomplishments throughout his career, beginning with his selection as Junior Research Fellow by the Indian Agricultural Statistics Research Institute (IASRI), 1977-1979. He received the American Statistical Association (ASA) Outstanding Statistical Application Award in 1997, and was elected a fellow of ASA in 2005. He is also an elected member of the International Statistical Institute.

Prior to joining the NIEHS Biostatistics Branch in 2000, Peddada pursued a 17-year career in higher education that culminated in his tenured appointment as a full professor at the University of Virginia. Since 2004, he has also served as an adjunct full professor of biostatistics at the University of North Carolina at Chapel Hill, and is also currently an adjunct professor of statistics at North Carolina State University.

Over the past ten years, Peddada has served on the editorial boards for several leading journals, including the Journal of the American Statistical Association, Toxicologic Pathology, and PLOS ONE. He is the author of more than 100 peer-reviewed publications.

Peddada completed a Bachelor of Science degree with honors in mathematics at the University of Delhi, and a Master of Science at IASRI in New Delhi, India. He earned his Master of Arts and Ph.D. at the University of Pittsburgh, where National Medal of Science winner Rao was Peddada's dissertation advisor.

Rao completed his own dissertation work at Cambridge University under the direction of Sir Ronald Fisher, a pioneering thinker Peddada described as one of the greatest statisticians of all time.

"My research program in constrained, or order-restricted, inference is influenced by Rao's interest in solving scientific problems by exploiting all available information," Peddada explained. "Many scientific problems have implicit constraints or structure, and by making use of such constraints, we arrive at solutions that not only honor the underlying structure, but also result in a powerful methodology."

During his nearly fifteen-year career as a government scientist, Peddada has taken advantage of that powerful methodology to advance environmental science research, working with teams of NIEHS and NTP epidemiologists, statisticians, biologists, and toxicologists.

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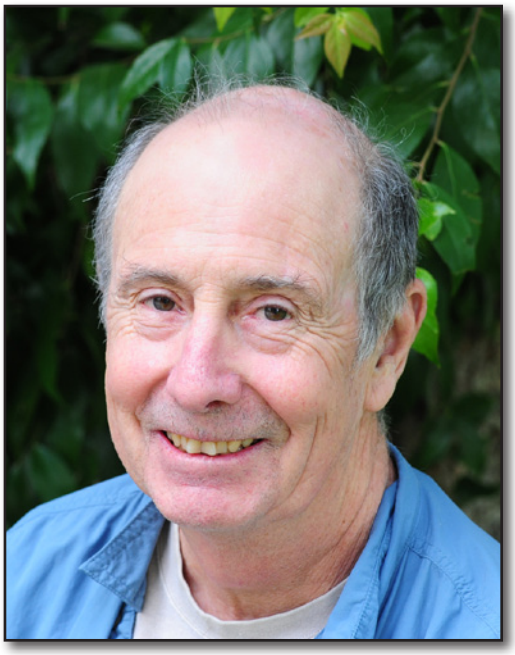
SRP grantee receives prestigious Brodie Award for contributions to drug metabolism research

By Sara Mishamandani

Bruce Hammock, Ph.D., a longtime NIEHS Superfund Research Program (SRP) grantee, was honored by the American Society for Pharmacology and Experimental Therapeutics (ASPET) with the biennial Bernard B. Brodie Award in Drug Metabolism. The award recognizes outstanding original research contributions in drug metabolism and disposition, particularly those having a major impact on future research in the field.



Hammock currently directs the UC Davis SRP, along with the National Institutes of Health Biotechnology Training Program and the NIEHS Combined Analytical Laboratory. (Photo courtesy of Kathy Garvey).

Hammock, who holds a joint appointment with the University of California (UC), Davis Department of Entomology and Nematology, and Comprehensive Cancer Center, joined the UC Davis faculty in 1980. He also directs the UC Davis Superfund Research Program (SRP), which has been continually funded since1987.

A leader in the field of drug metabolism

Hammock is best known for discovering the soluble epoxide hydrolase (sEH), a form of the epoxide hydolase enzyme that exists in the cell cytosol and degrades chemically stable fatty acid epoxides. This discovery had important implications for the development of therapeutic agents.

To investigate the biological role of this enzyme, his team created potent inhibitors. Inhibitors are commonly used to determine the location of the enzyme's active site and to study factors that control enzyme activity. They found that the potent inhibitors created to study sEH could be used in mouse and rat models as a drug to reduce inflammation and inflammatory pain more effectively than nonsteroidal anti-inflammatory drugs. Hammock has also explored the use of inhibitors of epoxide hydrolases as drugs to treat diabetes, ischemia, and cardiovascular disease.

He recently determined the molecular mechanism underlying the beneficial effects of inhibiting sEH after heart attacks, opening the doors for a new therapy to stop cardiac fibrosis (see story). He is even collaborating with veterinarians to test sEH inhibitors to treat laminitis, a painful and deadly disease in horses (see story).

The compounds are in efficacy trials for companion animals and in the investigational new drug enabling stage to assess potential interactions and metabolic stability before entering clinical trials.

In selecting Hammock, ASPET acknowledged Hammock for his collaborative studies in drug metabolism and metabolomics. Hammock is known for his tradition of identifying new collaborators and sharing reagents to enable investigators in both private and public sectors to make substantial advances in treating stroke, atherosclerosis, heart failure, renal failure, inflammation, and neuropathic pain.

Bruce is known for working hard and playing hard. In 2003, he launched an annual water balloon battle, 15 Minutes of Aim, to build camaraderie and gain relief from the heat. Hammock, right, loses a water balloon confrontation after SRP trainee Karen Wagner dumps the water filled bucket on him. (Photo courtesy of Kathy Garvey).

A long history with NIEHS

Author of more than 900 peer-reviewed publications and member of the National Academy of Sciences, Hammock is a leader in his fields of research. His team of more than 40 scientists and students delves into basic questions of biology and biochemistry that have practical implications for improving both human and environmental health.

Before beginning his relationship with NIEHS SRP in 1987, Hammock received partial support from NIEHS for his graduate education at UC Berkeley. He also received an NIEHS merit award in 1998. Trained as an insect developmental biologist, Hammock expanded his research interests to include drug development and advanced laboratory analysis.

His SRP-funded laboratory also pioneered the use of immunoassay technologies to detect hazardous chemicals, developing a way to test for the presence of pyrethroids, a class of pesticides.

Hammock will receive the award and present a keynote speech about his research Apr. 28 in San Diego at the annual joint meeting of ASPET and the Chinese Pharmacological Society.

(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.)

At UC Davis, Hammock teaches in the Pharmacology and Toxicology Graduate Group. Seen above conquering the rapids, he also teaches whitewater kayaking. (Photo courtesy of Bruce Hammock)

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Science Notebook

Meeting on mammalian transgenerational inheritance fosters collaboration

By Jacqueline Powell

The NIEHS Division of Extramural Research and Training (DERT) hosted the Transgenerational Inheritance in Mammals after Environmental Exposure (TIME) grantee meeting Feb. 12-13. Lisa Helbling Chadwick, Ph.D., health scientist administrator in the NIEHS Genes, Environment, and Health Branch, organized the gathering of twenty experts in the field.

A graphic for the TIME grantee meeting illustrates the concept of transgenerational inheritance, as exposures in utero (F0) may affect offspring in succeeding generations.

With predictions for severe winter weather on the day of the meeting, Chadwick and colleagues made a prudent decision to circumvent transportation-related issues by moving the meeting site from the NIEHS Rodbell auditorium to a nearby hotel, where many of the attendees were staying. While the weather created some hardships for visitors and prevented several of the presenters from traveling to the meeting, each enjoyed an opportunity to learn about others' research and present their own work through teleconferencing.

Chadwick is also involved in other NIEHS research initiatives related to transgenerational inheritance, including Developmental Origins of Health and Disease, Environmental Epigenetics, and the NIH Roadmap Epigenomics Program. (Photo courtesy of Steve McCaw)

Along with NIEHS-funded researchers, scientists with the NIEHS Division of Intramural Research and Division of the National Toxicology Program attended in person and by phone, signifying the high level of interest in this topic and program across all parts of the Institute's research community.

The TIME program is focused on how adverse consequences of environmental toxicant exposure can be transmitted from one generation to the next, ultimately affecting multiple generations beyond the original insult. These adverse effects of environmental exposure can occur through transgenerational inheritance, which refers to heritable changes in gene activity that are typically introduced by epigenetic modifications.

Aligning transgenerational research with the NIEHS strategic plan

"The program is getting off to a much better start than the meetings are," said Gwen Collman, Ph.D., DERT director, referring to cancellation of the original meeting because of the government shutdown in October 2013. "We hope not to have you [in North Carolina] longer than you intend to stay."

Collman then emphasized how research being conducted on transgenerational inheritance is linked to understanding how environmental factors influence individual susceptibility to chronic complex diseases across the lifespan, a priority for NIEHS-sponsored environmental health research as articulated in the Institute's strategic plan.

"One of the key goals of the meeting is to try and identify opportunities for collaboration among groups so that we can maximize the amount of information we can get from these [multigenerational animal] studies," said Chadwick. Other goals for the meeting included having discussions on optimizing study designs and coordinating outreach activities to explain the emerging concept of transgenerational inheritance to the scientific community and lay public.

In her remarks, Collman pointed to goal 2 in the NIEHS strategic plan, which involves support of research into understanding individual susceptibility to environmental exposures across the human lifespan. Research has clearly established the effects of early life exposure, she said, but a question remains for researchers — "Do they persist through future generations?" (Photo courtesy of Steve McCaw)

Highlighting divergent approaches to transgenerational inheritance

The conference began with a talk by Marisa Bartolomei, Ph.D., professor of cell and developmental biology at the Perelman School of Medicine at the University of Pennsylvania, on the transgenerational effects of bisphenol A (BPA), a known endocrine disruptor. This research is providing insight into mechanisms that may be explored in humans.

Mapping the transgenerational effects of environmental exposures

In addition to the presentations by Bartolmei, Puga, Vorhees, and Rubenstein that opened and closed the information-packed morning session, representatives from other transgenerational inheritance projects presented their preliminary findings.

- David Crews, Ph.D., spoke by phone about work he and Andrea Gore, Ph.D., are directing on "Ancestral Exposures/Modern Responses to EDCs [Endocrine Disrupting Compounds]" at the University of Texas at Austin.
- University of Rochester graduate student Lisbeth Boule outlined research conducted by her group, led by Paige Lawrence, Ph.D., exploring "Transgenerational Exposures as Modifiers of Host Defense Against Infection."
- Harvard School of Public Health researcher Lester Kobzik, M.D., described his work on "Transgenerational Susceptibility to Asthma From Air Pollution Exposure" in collaboration with Alexey Fedulov, M.D., Ph.D.
- Massachusetts General Hospital physician-scientist Toshihiro Shioda, M.D., Ph.D., reported on his collaboration with University of California, Irvine researcher Bruce Blumberg, Ph.D., on "Transgenerational Inheritance of Prenatal Obesogen Exposure."
- Speaking by phone from her office at the University of California, San Francisco, Diana Laird, Ph.D., outlined her group's work on "Assessing Transgenerational Effects of Phthalates on Primordial Germ Cells."

Another presentation led by Alvaro Puga Ph.D., professor at University of Cincinnati (UC) College of Medicine, described a cross-disciplinary approach to investigate the transgenerational effects of exposure to polychlorinated biphenyls (PCBs). Collaborating with neurobiologist Charles Vorhees, Ph.D., professor at the Cincinnati Children's Hospital Medical Center, and cardiologist Jack Rubenstein M.D., assistant professor at UC College of Medicine, they were able to examine the effect of PCB exposure on DNA methylation, neurophysiology, and cardiovascular function.

The research presented at the meeting examined exposure to a variety of endocrine disrupting chemicals including BPA, tributyltin, diesel exhaust particles, phthalates, and polychlorinated biphenyls. The array of endpoints being examined was also impressive, including assessments of DNA methylation status, body weight, glucose regulation, immune cell function, learning, and cardiac function. Given the wide array of exposure paradigms and endpoints presented, it is clear that collaborations between investigators have great potential to advance the field.

(Former NIEHS postdoctoral fellow Jacqueline Powell, Ph.D., is a writer and analyst with Education and Training Systems International.)

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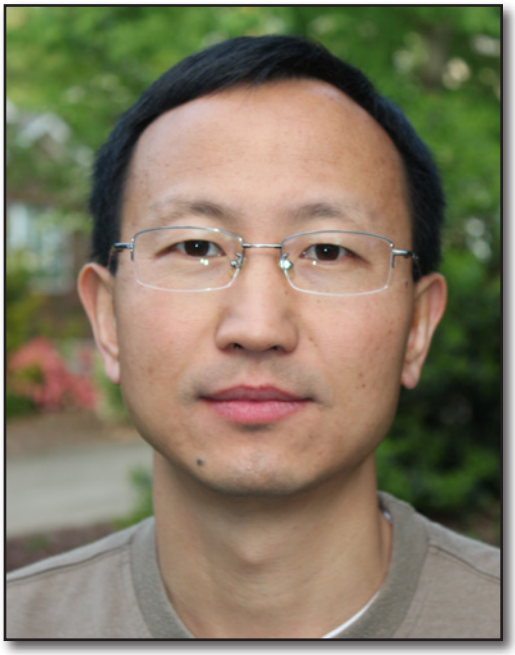
NIEHS study offers insight into why cancer incidence increases with age

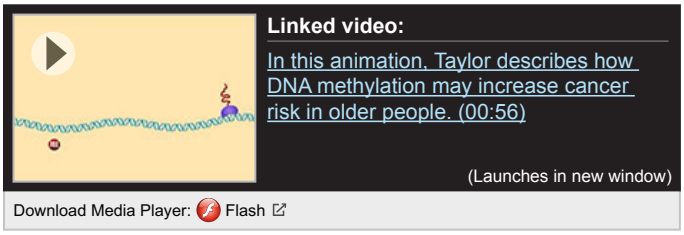
By Robin Arnette

Scientists have known for years that age is a leading risk factor for the development of many types of cancer, but why aging increases cancer risk remains unclear. In a study published in the February issue of the journal Carcinogenesis, researchers from the NIEHS Epidemiology Branch, Zongli Xu, Ph.D., and Jack Taylor, M.D., Ph.D., identified DNA methylation sites across the human genome that changed with age.

Researchers have suspected that DNA methylation, or the binding onto DNA of chemical tags called methyl groups, may be involved in the increase of cancer incidence with age. Methyl groups activate or silence genes by affecting interactions between DNA and the cell's protein-making machinery. Xu and Taylor demonstrated that a subset of those sites — the ones that become increasingly methylated with advancing age — are also disproportionately methylated in a variety of human cancers.



Xu is a staff scientist in the NIEHS Epidemiology Branch. (Photo courtesy of Zongli Xu)



"You can think of methylation as dust settling on an unused switch, which then prevents the cell from turning on certain genes," Taylor said. "If a cell can no longer turn on critical developmental programs, it might be easier for it to become a cancer cell."

Taylor holds appointments in the NIEHS Epidemiology Branch and the Molecular Carcinogenesis Laboratory. (Photo courtesy of Steve McCaw)

Age-related methylation and tumor growth

Xu and Taylor made the discovery using blood samples from participants in the Sister Study, a nationwide research effort to find the environmental and genetic causes of breast cancer and other diseases. More than 50,000 sisters of women who have had breast cancer are participating in the study.

The researchers analyzed blood samples from 1,000 women, using a microarray that contained 27,000 specific methylation sites. Nearly one-third of the sites showed increased DNA methylation in association with age. They then looked at three additional data sets, from smaller studies that used the same microarray, and found 749 methylation sites that behaved consistently across all four data sets. As an additional check, they consulted methylation data from normal tissues and seven different types of cancerous tumors in The Cancer Genome Atlas, a database funded by the National Cancer Institute and the National Human Genome Research Institute.

Taylor said that DNA methylation appears to be part of the normal aging process and occurs in genes involved in cell development. Cancer cells often have altered DNA methylation, but the researchers were surprised to find that 70-90 percent of the sites associated with age showed significantly increased methylation in all seven cancer types. Taylor suggests that age-related methylation may disable the expression of certain genes, making it easier for cells to transition to cancer.

Understanding how the environment affects methylation

The research also determined how fast these methylation events accumulate in cells. They occur at a rate of one per year, according to Xu.

"On your 50th birthday, you would have 50 of these sites [from the subset of 749] that have acquired methyl groups in each cell," Xu said. "The longer you live, the more methylation you will have."

For future work, Xu and Taylor want to examine more samples, using a newer microarray that will explore methylation at 450,000 genomic methylation sites. The additional samples and larger microarray, which will provide 16 times more genomic coverage, will allow them to address whether environmental exposures during adulthood or infancy affect methylation profiles. These additional studies will help scientists better understand why methylation happens as people march toward their retirement years.

DNA methylation is one of several epigenetic mechanisms that can control gene expression without changes in DNA sequence. This study is part of a broader research effort, funded by NIEHS, to understand how environmental and other factors affect epigenetic mechanisms in relation to health.

Citation: Xu Z, Taylor JA. 2014. Genome-wide age-related DNA methylation changes in blood and other tissues relate to histone modification, expression, and cancer. Carcinogenesis 35(2):356-364.

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Council briefed on Parkinson's premotor symptoms research

By Ernie Hood

At the Feb. 19-20 meeting of the NIEHS National Advisory Environmental Health Sciences Council, panel members were treated to a talk by Honglei Chen, M.D., Ph.D., head of the Aging and Neuroepidemiology Group.

Chen, who was recently awarded tenure (see story), updated the council on his group's research into the clinical implications of premotor symptoms in Parkinson's disease, and the potential for better understanding what causes the disease.

"We've made a lot of progress in understanding the etiology of Parkinson's. We've learned of many genetic risk factors from recent GWAS studies, and we've also identified a number of nongenetic or environmental risk factors for Parkinson's," Chen noted in his remarks to the council. (Photo courtesy of Steve McCaw)

Major disease, major unmet need

As Chen related, Parkinson's disease is the second most prevalent neurodegenerative disease after Alzheimer's, afflicting more than 1 percent of the U.S. elderly population at an annual cost of $23 billion. Current therapies can help control symptoms, but there is no cure for Parkinson's, and no therapy to stop or even slow disease progression.

Parkinson's may develop over the course of decades, and by the time the motor symptoms appear allowing definitive diagnosis, it is too late for any effective intervention. Motor signs include slow physical movements, shaking, muscle stiffness, and impaired balance and coordination.

Thus, Chen focuses his research on the premotor, or prodromal, symptoms of Parkinson's, striving to answer the fundamental questions of when, where, and how Parkinson's disease starts.

"There is no dispute that the motor signs of Parkinson's are just the tip of the iceberg, and that patients suffer from a variety of very prominent nonmotor symptoms," Chen said. "These symptoms may precede the onset of Parkinson's motor signs by years. We call these the premotor symptoms of Parkinson's."

Identifying patients with premotor symptoms can give some indication of who will be at risk for Parkinson's and pinpoint a window of time when new interventions may work to prevent or delay full onset. This could also increase understanding of the early disease process of Parkinson's, which has been largely uncharted thus far. That is especially true for environmental risk factors, which are strongly suspected to combine with genetic risk factors to increase risk of Parkinson's and may be a point of therapeutic attack.

One of Chen's research methods is the Sniffin' Sticks™ smell test, in which participants are asked to smell and identify twelve common odors such as banana, coffee, rose, and fish. A score of 6 or less indicates anosmia, or loss of sense of smell, one of the premotor symptoms of Parkinson's disease. (Image courtesy of Honglei Chen)

Premotor symptoms appear much earlier

The most important premotor symptoms of Parkinson's may appear as early as 20 years prior to the onset of motor symptoms. They include loss of smell, rapid eye movement sleep behavior disorder, constipation, daytime sleepiness, depression, and anxiety. Chen emphasized that it is important to study the entire group of premotor symptoms, since individually they are often nonspecific.

"The key concept is not one single, particular symptom, but rather to look at multiple symptoms and future risk for Parkinson's," he said. In one unpublished case-control study Chen described, individuals with three of the six premotor symptoms were 31 times more likely to have Parkinson's than controls. That data also suggested a potential gender difference, with a stronger association in men than women.

According to Chen, in the past 10 years, substantial evidence has accumulated that premotor symptoms occur prior to diagnosis of Parkinson's. His work will continue and expand in the future.

"My overall approach will be to study the disease from the beginning to the end, trying to identify an intermediate phenotype that can help us identify high-risk populations," he said. "We particularly want to study what environmental factors can modify this process, from the high-risk population to final Parkinson's disease, and try to understand what environmental factors can give rise to these symptoms."

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

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NIEHS-funded scientists say more chemicals linked to neurodevelopmental disorders

By Joe Balintfy

Based on a review of current published research, scientists funded by NIEHS have identified several additional industrial chemicals documented in scientific literature as toxic to brain development and the human nervous system. In a new study published in the journal Lancet Neurology, the authors suggested that compounds including metals, solvents, and pesticides may be partially responsible for the increased prevalence of neurodevelopmental disorders in children.

Neurodevelopmental disorders include autism, attention-deficit hyperactivity disorder, dyslexia and other cognitive impairments.

This study is a follow-up to the authors' 2006 study. The current paper discusses six more industrial chemicals they found documented in scientific literature as toxic to brain development (listing provided in table 1 below), and 12 more which research has shown as toxic to the adult human nervous system (listing provided in table 2 below).

Grandjean said that methods are in place to test industrial chemicals for harmful effects on children's brain development. (Photo courtesy of Harvard School of Public Health)

The developing brain and chemical exposures

The researchers emphasized in their paper that the developing brain is uniquely vulnerable to toxic chemical exposures.

"We need a new paradigm of action to protect the brain development of the next generation," said Philippe Grandjean, M.D., adjunct professor of environmental health at the Harvard School of Public Health. "I believe children worldwide are exposed to thousands of untested chemicals."

"In only seven years, the number of industrial chemicals recognized to have impacts on brain development has doubled," added Philip J. Landrigan, M.D., M.Sc., the Ethel H. Wise Professor of Preventive Medicine, Chair, Department of Preventive Medicine, and Director of the Children's Environmental Health Center at the Icahn School of Medicine at Mount Sinai.

They wrote in their paper that new data have emerged about both the vulnerability of the developing brain and the neurotoxicity of industrial chemicals. They explained that epidemiological birth cohort studies are a source of this new data.

Landrigan recommended a precautionary approach to testing of existing and new chemicals. (Photo courtesy of Icahn School of Medicine at Mount Sinai)

"It's important that policy decisions should be based on the most current scientific research available," said Linda Birnbaum, Ph.D., director of NIEHS and the National Toxicology Program. She said this study could help guide continuing efforts to evaluate chemicals as mandated by the federal Toxic Substances Control Act (TSCA). "Science has seen a lot of advances since TSCA was enacted in the 70s, including new methods and technologies to conduct research. This paper, and its examination of current research, lends support to the need for a fresh perspective on chemical evaluation."

Looking at lots of chemicals

The researchers also noted that dealing with mixed exposures is a problem. They wrote that most populations are exposed to several chemicals, pollutants, and other environmental agents simultaneously, yet most studies only have enough power and precision to discern effects of a single exposure at a time. "For many years we've looked at individual agents, but now are beginning to successfully estimate risk from combinations of exposures," Birnbaum added. "No one is exposed to just one chemical."

	Known in 2006	Newly identified
Metals and inorganic compounds	Arsenic and arsenic compounds, lead, and methylmercury	Fluoride and manganese
Organic solvents	(Ethanol) toluene	Tetrachloroethylene
Pesticides	None	Chlorpyrifos and DDT/DDE
Other organic compounds	Polychlorinated biphenyls	Brominated diphenyl ethers
Total	6*	6

DDT=dichlorodiphenyltrichloroethane. DDE=dichlorodiphenyldichloroethylene. *Including ethanol.

Table 1: Industrial chemicals researchers documented as toxic to brain development in human beings in 2006 and 2013, grouped by chemical type. (Courtesy of Lancet Neurology)

	Number known in 2006	Number known in 2013	Identified since 2006
Metals and inorganic compounds	25	26	Hydrogen phosphide[82]
Organic solvents	39*	40	Ethyl chloride[83]
Pesticides	92	101	Acetamiprid,[84] amitraz,[85] avermectin,[86] emamectin,[87] fipronil (Termidor),[88] glyphosate,[89] hexaconazole,[90] imidacloprid,[91] tetramethylenedisulfotetramine[92]
Other organic compounds	46	47	1,3-butadiene[93]
Total	202*	214	12 new substances

*Including ethanol.

Table 2: Industrial chemicals researchers documented as toxic to the human nervous system in 2006 and 2013, grouped by chemical type. (Superscripts refer to the reference list of the published paper. Table courtesy of The Lancet Neurology.)

Press releases on the study were released by The Lancet, Harvard School of Public Health, and Icahn School of Medicine at Mount Sinai.

Citation: Grandjean P, Landrigan P. 2014. Neurobehavioural effects of developmental toxicity. Lancet Neurol; doi:10.1016/S0140-6736(08)61345-8 [Online 14 February 2014].

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

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Research on dopamine and Parkinson's disease illustrates value of exposome studies

By Annah Wyss

In a Feb. 5 seminar, "Reducing Neurotoxicity by Increasing Vesicular Capacity," hosted by the NIEHS Laboratory of Neurobiology, Gary Miller, Ph.D., professor and associate dean for research at Emory University's Rollins School of Public Health, described his laboratory's NIEHS-funded research on dopamine and Parkinson's disease.

Specifically, Miller's group is studying how the alteration of the storage of dopamine, a neurotransmitter, may contribute to Parkinson's disease, a neurodegenerative disorder characterized by motor symptoms, such as tremors and slowed movement, and nonmotor symptoms, such as changes in cognitive abilities and mood. Disrupted storage of dopamine leads to the degeneration of dopamine neurons in the brain.

Pesticides, such as paraquat, and polychlorinated biphenyls (PCBs) have been linked to Parkinson's. Although many of these chemicals are now banned, they persist in the environment, causing continued human exposure. Since PCBs are known to inhibit storage of dopamine, characterizing the physiological effects of inhibited transport of dopamine may have important implications for understanding Parkinson's disease.

Regulation of dopamine linked with proteins VMAT2 and SV2C

Miller highlighted his lab's research on vesicular monoamine transporter 2 (VMAT2), a protein that helps regulate dopamine. Among mice with 90 percent reduced VMAT2 levels, Miller's group observed low levels of stored dopamine in vesicles. These mice were further characterized by overexpression of alpha-synuclein, a protein previously associated with Parkinson's disease, and exhibited symptoms similar to Parkinson's disease.

On the other end of the spectrum, mice with overexpressed VMAT2 appeared to be slightly more active and had vesicles that stored and released higher levels of dopamine, compared to wild-type mice.

Miller also described his research on synaptic vesicle glycoprotein 2C (SV2C), and the impact of the genetic deletion of SV2C. In discussing the motivation to study SV2C, Miller referenced other research on Parkinson's disease.

"Our interest in SV2C came from a genome-wide association study (GWAS) that integrated an environmental factor. Otherwise we wouldn't be looking at it," he explained.

Miller's research demonstrates the effect of proteins VMAT2 and SV2C on vesicular storage of dopamine, offering insights into the relationship between pesticides and Parkinson's disease. (Photo courtesy Gary Miller)

Studying the exposome to advance public health

Miller also promotes the integration of environmental and genetic research as director of Emory University's Health and Exposome Research Center: Understanding Lifetime Exposures (HERCULES), an NIEHS Environmental Health Sciences Core Center. The center concentrates on studying the exposome, which Miller defines as the cumulative effect of environmental exposures on health over a lifetime.

"It is not just the exposures — it is how we respond to them," Miller reminded the audience. He said he hopes that efforts to understand the exposome will provide a set of tools to complement genomics analysis and provide a more comprehensive assessment of health outcomes, including the cause of Parkinson's disease.

(Annah Wyss, Ph.D., is an Intramural Research Training Award (IRTA) postdoctoral fellow with the Genetics, Environment, and Respiratory Disease Group.)

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Study finds a new marker for assessing heart inflammation

By Sheila Yong

You might not think to look to the brain to measure inflammation in the heart. Yet, NIEHS grantee Tomás Guilarte, Ph.D., discovered that a widely used biomarker for diagnosing brain injury can also help determine the severity of heart inflammation — a condition known as myocarditis.

Funded in part by NIEHS, Guilarte's findings were published Jan. 9 online in the Journal of Cardiovascular Translational Research.

Revolutionizing the assessment of heart inflammation

Guilarte, professor and chair of environmental health sciences at the Columbia University Mailman School of Public Health, has been studying the translocator protein 18 kDa (TSPO) for almost two decades. His previous research established TSPO as a clinical biomarker for brain injury and neurodegeneration. The advantage of TSPO is that it can be imaged and quantitatively measured in the living human brain or in experimental animals, using noninvasive techniques, such as positron emission tomography (PET) and single-photon emission computed tomography (SPECT).

Guilarte is also a member of the NIEHS National Advisory Environmental Health Sciences Council. (Photo courtesy of Steve McCaw)

The findings from Guilarte's brain studies led him to wonder if TSPO could also be used to examine inflammation in other organs, such as the heart. To address this possibility, Guilarte and his collaborators assessed TSPO levels in tissues obtained from myocarditis patients and mice. The mice had been previously exposed to coxsackievirus B3, which often causes myocarditis in humans. Using SPECT, the researchers found higher levels of TSPO in male mice compared to healthy controls.

SPECT can directly measure the extent of inflammation in the heart, without a biopsy or extensive surgical procedures. This is because when the heart is inflamed, it becomes filled with immune cells expressing the CD11b marker, the same cells that also express high levels of TSPO.

The clinical implications of TSPO levels in the heart

Interestingly, the researchers also observed a gender difference in TSPO expression — male patients and male mice with myocarditis expressed higher levels of TSPO than their female counterparts. Further experimentation with myocarditis mice revealed that the male hormone, testosterone, increases TSPO expression during myocarditis, specifically in the immune cells in the heart. Hence, the authors concluded that testosterone amplifies the inflammation, leading to permanent heart damage and failure. These findings also explain why men are at greater risk for myocarditis and other heart conditions related to inflammation.

Guilarte is excited about integrating his TSPO findings from the brain and heart studies to better understand the clinical implications of TSPO expression. "Our latest study is a major milestone, because it demonstrates that we can take what we learned about TSPO in the brain and draw lessons for the heart," Guilarte said in a Columbia University press release. "At the same time, we should be able to take what we are learning about TSPO in the heart and apply it to our continuing TSPO research in the brain."

Guilarte believes there is a huge potential for how TSPO can impact not only myocarditis, but also cardiovascular diseases in general. "We have evidence that we can slow down neurodegeneration by controlling levels of TSPO in the brain," he explained. "This approach may eventually prove to have therapeutic value in the heart as well."

Annette Kirshner, Ph.D., NIEHS Division of Extramural Research and Training program administrator for Guilarte's funding, is impressed with his accomplishments in TSPO research. "TSPO is an exceptional molecular biomarker of brain injury and inflammation that can also be used to assess recovery from injury and the effectiveness of therapeutic strategies," she said. "Since TSPO is found in many regions of the body, expanding the use of this biomarker is very exciting."

The researchers plan to conduct a clinical trial at the Mayo Clinic, to see if TSPO can detect myocarditis-related inflammation in patients with the condition. Their ultimate goal is to develop a reliable diagnostic method for myocarditis that can replace current procedures, which are often invasive and less accurate.

Citation: Fairweather D, Coronado MJ, Garton AE, Dziedzic JL, Bucek A, Cooper LT Jr, Brandt JE, Alikhan FS, Wang H, Endres CJ, Choi J, Pomper MG, Guilarte TR. 2014. Sex differences in translocator protein 18 kDa (TSPO) in the heart: implications for imaging myocardial inflammation. J Cardiovasc Transl Res; doi:10.1007/s12265-013-9538-0 [Online 9 January 2014].

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

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NIEHS-funded research shows link between DDT and Alzheimer's disease

By Joe Balintfy

Researchers, funded in part by NIEHS, have made progress in connecting the dots between exposure to the pesticide DDT and risk for Alzheimer's disease. The results of a study published Jan. 27 in the journal JAMA Neurology may help lead to a screening test for Alzheimer's susceptibility in certain people, according to the authors.

Jason Richardson, Ph.D., associate professor at Rutgers Robert Wood Johnson Medical School, said Alzheimer's is the most common neurodegenerative disease in the world, and the number of cases are expected to explode over the next 20-30 years.

"As with many neurological disorders, many [Alzheimer's] studies focused on genetic susceptibility," he said. "Our study is one of the first that really demonstrates that there may be an environmental influence — specifically that DDT or DDE exposure may have an association."

According to Richardson, one problem with Alzheimer's disease is that, often, by the time patients are diagnosed, the disease has progressed to a point where therapeutic interventions are very limited. (Photo courtesy of Jason Richardson)

Listen as Richardson discusses DDT exposure and genetic risk factors for Alzheimer's disease. (0:52)

Read Transcript

DDT in the blood and genetic risk

Although banned in the U.S. in the 1970s, DDT lingers in the environment — what Richardson calls legacy contamination — and continues to be used elsewhere in the world. Exposure to DDT can be measured by checking blood levels of DDE, a breakdown product of DDT.

Researchers found DDE levels to be 3.8 times higher in blood samples of Alzheimer's patients compared to controls. According to the study, those with the highest DDE levels were associated with an even higher risk of developing Alzheimer's. The study involved 86 Alzheimer's patients and 79 controls at two study sites.

Richardson said that, based on the data from his research, he may be considered at higher risk for Alzheimer's. "I grew up a farm kid in Louisiana and Mississippi. I applied pesticides. "So, this is something that's kind of near and dear to my heart on a number of levels."

According to Richardson, people carrying the apolipoprotein E (APOE) E4 form of a gene — a leading indicator of a person's risk of getting late-onset Alzheimer's — may be more susceptible to the effects of DDT and DDE. "What our data suggest is that if you do have high levels of DDE in your blood, and you have an APOE E4 allele, you may have worse cognitive function."

Connecting the dots between DDT and Alzheimer's

Scientists are increasingly finding that neurodegenerative diseases, such as Alzheimer's, have an environmental link. "This is building on the evidence that the causes of Alzheimer's disease are a combination of genes and the environment," said Annette Kirshner, Ph.D., health scientist administrator in the NIEHS Genes, Environment, and Health Branch.

Richardson said the new study builds on a 2009 study of pesticides and Parkinson's disease. "In that study," he explained, "we used 20 Alzheimer's cases as kind of a disease control group." While the organochlorine pesticide the researchers studied was associated with increased risk of Parkinson's disease, it was not associated with Alzheimer's. "But in those 20 [Alzheimer's] patients, we found elevated DDE levels."

He cautioned that the new study has limitations. "If you compare it to the genetic studies where you have thousands and thousands of patients and controls, ours is relatively small." But, Richardson pointed out that, for this study, researchers took an extra step. "Even though we can't prove causality, we tried to take it one step further, asking if there is a mechanistic link between DDT and DDE and Alzheimer's disease. What we show in the paper is that if you expose cultured cells to DDT or DDE at levels that have been observed in highly exposed people in the United States, you actually cause an increase in a protein that is linked with Alzheimer's disease."

This study was highlighted in a Jan. 27 article in Research News at Rutgers.

Citation: Richardson JR, Roy A, Shalat SL, von Stein RT, Hossain MM, Buckley B, Gearing M, Levey AI, German DC. 2014. Elevated serum pesticide levels and risk for Alzheimer disease. JAMA Neurol; doi:10.1001/jamaneurol.2013.6030 [Online 27 January 2014].

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

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Genetic variation may explain PCB-resistance in Atlantic killifish

By Sara Mishamandani

Changes in a receptor protein may explain how killifish evolved genetic resistance to polychlorinated biphenyls (PCBs) in New Bedford Harbor, Mass., according to a new study published in BMC Evolutionary Biology. New Bedford Harbor, one of the largest U.S. Environmental Protection Agency (EPA) Superfund cleanup sites, is heavily contaminated with PCBs and heavy metals.

Despite the substantial pollution, Atlantic killifish, a small fish common to estuaries, are thriving in the toxic conditions. Researchers at the Woods Hole Oceanographic Institution (WHOI), led by Boston University

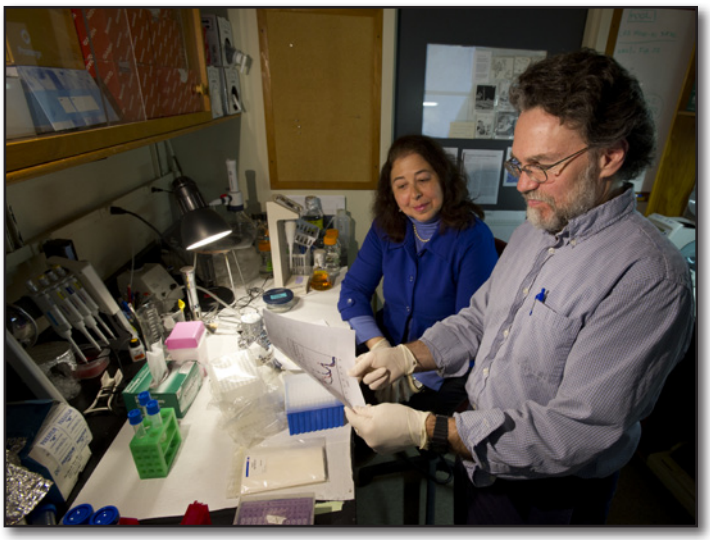
Superfund Research Program (SRP) grantee Mark Hahn, Ph.D., are collaborating with investigators at the EPA, the Boston University School of Public Health, and the University of North Carolina at Charlotte to understand how killifish have been able to adapt to live in the highly contaminated environment.

Investigating genetic variation in killifish

The researchers examined diversity in three specific genes, or loci, related to the aryl hydrocarbon receptor (AHR) in killifish from seven different locations, including extremely polluted estuaries as well as reference estuaries with low levels of PCB pollution.

Among all populations, investigators identified 98 variations in single DNA bases, or single nucleotide polymorphisms (SNPs), within the three AHR-related loci. However, they did not find significantly different genetic diversity at contaminated sites compared to reference sites.

But when they looked specifically at the New Bedford Harbor killifish population, they found significant genetic differences from the populations at two nearby reference sites. The data also revealed changes in specific nucleotides in AHR loci, and specific AHR2 SNPs associated with the PCB-resistant phenotype.



"Even though the specific molecular changes that are found in PCB-resistant killifish are different, AHR2 seems to be one of the genes — possibly the major gene — that is responsible for the resistance," said Hahn. Hahn, right, examines data with WHOI biologist Diana Franks, left, a co-author on the paper. (Photo courtesy of Tom Kleindinst, Woods Hole Oceanographic Institution)

According to the authors, the results revealed that AHRs, especially AHR2, may be recurring targets for selection during local adaptation of fish to contaminants, although the specific molecular changes may vary among independently adapting populations or species. Other genes, not yet identified, may also have a role in the adaptation.

"It's a fascinating example of how human activities can drive evolution," said Hahn. "The ability to adapt to changing conditions is going to become even more important as humans impact the environment, whether it's from ocean acidification, or increasing temperatures, or other types of global changes that are occurring."

The AHR2 pathway

Normally, when fish are exposed to toxicants, the body increases production of enzymes to break down the harmful chemicals, a process controlled by the AHR2 protein. However, some PCBs cannot be broken down this way, and continue to stimulate the AHR2 pathway. This continued stimulus leads to a disruption of cellular functions, such as the control of cell growth and differentiation.

"These killifish have managed to shut down the AHR2 pathway," said Hahn. "It's an example of how some populations are able to adapt to changes in their environment — a snapshot of evolution at work."

A companion paper by EPA collaborators, also published in BMC Evolutional Biology, examined SNPs from 42 genes associated with AHR-related pathways. The authors identified AHR2 as a gene under selection in resistant populations and suggested that AHR2 plays an important role in the adaptive response to extreme contamination of PCBs and other compounds with similar structures.

"Obviously, the fact that they are resistant to PCBs allows them to survive in this really polluted environment, but what will happen once the harbor gets cleaned up? There could be costs that make it no longer adaptive for these fish to live there," said Hahn.

Atlantic killifish, only about three inches long, live their whole lives in the same area and do not migrate south for the winter. In New Bedford Harbor, they burrow into PCB-contaminated sediment for the winter. (Photo courtesy of Evan D'Alessandro, University of Miami)

Citation: Reitzel AM, Karchner SI, Franks DG, Evans BR, Nacci D, Champlin D, Vieira VM, Hahn ME. 2014. Genetic variation at aryl hydrocarbon receptor (AHR) loci in populations of Atlantic killifish (Fundulus heteroclitus) inhabiting polluted and reference habitats. BMC Evol Biol. 14(1):6; doi:10.1186/1471-2148-14-6.

Citation: Proestou DA, Flight P, Champlin D, Nacci D. 2014. Targeted approach to identify genetic loci associated with evolved dioxin tolerance in Atlantic Killifish (Fundulus heteroclitus). BMC Evol Biol. 14(1):7; doi:10.1186/1471-2148-14-7.

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

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New approaches in mustard gas exposure treatment

By Monica Frazier

As part of the Keystone Science Lecture Seminar Series, highlighting the broad range of research by its grantees, NIEHS hosted a talk Feb. 6 by pediatric pulmonologist Carl White, M.D. His current research, funded by the NIH Countermeasures Against Chemical Threats (CounterACT) program, focuses on the prevention and treatment of respiratory damage from exposure to the toxic vesicants, or blistering agents, sulfur, nitrogen, mustards, and chlorine gas.

White described his research group's progress in the treatment of mustard-gas exposed rodents to a group of NIEHS and NTP researchers, many of them from the Laboratory of Respiratory Biology. (Photo courtesy of Steve McCaw)

The presentation, "Novel Countermeasures Against Chemically Induced Airways Injury," outlined the progress White's group has made toward mustard gas post-exposure therapeutics. According to White, mustard gas was one of the deadliest chemical agents used in World War I, and still poses a chemical threat to public health through accidental spill, terrorist attack, or use by military forces in countries such as Libya and Syria, which still have significant stockpiles.

White is a professor of pediatrics and director of the Pediatric Airway Research Center, as well as director of the CounterACT Center of Excellence at the University of Colorado (UC) Denver.

The continuing threat of mustard gas

Although sometimes thought of as a weapon that is out of date, mustard gas maintains a presence in many countries for use as a chemical weapon. as well as in depots for eventual disposal, such as ones in Pueblo, Colo., and elsewhere.

NIH CounterACT funding promotes the development of countermeasures against chemical warfare threats, such as mustard gas. Surprisingly, even nearly a century after development of mustard gas, the best treatment for exposure has not been definitively determined, which is exactly what White aims to do.

White detailed his research program during the lecture, saying, "[Its goals are] to develop or optimize anticoagulants, fibrinolytics, and catalytic antioxidants to rescue or prevent airway injury or death due to vesicants."

As Sri Nadadur, Ph.D., program director overseeing the CounterACT program at NIEHS, explained in his introduction, "The research effort on the use of fibrinolytics as a countermeasure for sulfur mustard-induced pulmonary injury is promising and going in the right direction."

Nadadur hosted White's talk, introducing White and monitoring the question-and-answer session that followed. (Photo courtesy of Steve McCaw)

Effective post-exposure treatments with FDA approved drugs

Airway occlusions, a type of blockage of normal respiration, are often seen in mustard gas-exposed patients as a result of fibrin lesions or casts. White and his colleagues have found some of the same fibrinolytic drugs, already approved by the U.S. Food and Drug Administration (FDA) to treat strokes, myocardial infarction, and other conditions, to be extremely beneficial in rats exposed to mustard gas. For example, treatment post-exposure with tissue plasminogen activator (tPA) shows impressive results, including markedly better oxygen saturation, clinical scores, and survival rates.

In addition to tPA, tissue factor pathway inhibitor (TFPI) and heparin, which is commonly used in children affected with plastic bronchitis, are also being investigated as therapeutics. In the heparin-treated group, considerable relief of symptoms was seen with treatment every four hours, and full survival at 48 hours, but White made a point that the treatments were started early after exposure.

In addition to their 48-hour studies, White and colleagues are performing 28-day studies with a broad-spectrum catalytic antioxidant, AEOL 10150. "This is the first nonairway administered drug that we've been able to find that has efficacy in the sulfur mustard model," he said.

University of Texas Southwestern Medical Center clinical researcher Rashmin Savani, M.D., right, was on hand as a guest of Stavros Garantziotis, M.D., left, acting director of the NIEHS Clinical Research Program and NIEHS Clinical Research Unit Medical Director. (Photo courtesy of Steve McCaw)

Despite significant improvement in the treated rodents, survival after 48-72 hours is not yet ideal without continued treatment. In the future, White hopes to move into a second species to test rescue drugs, or quick relief medications, so that his group can begin to focus on how to manage treatment with chronic disease in surviving patients.

Future studies at UC Denver and the U.S. Army Research Laboratory at the Aberdeen Proving Ground in Maryland, will explore the health effects of lower doses of mustard gas, and develop models for mustard gas inhalation to test effects of chlorine gas exposure.

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

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NIEHS study on genome stability highlighted in Genetics

By Staton Wade

The negative impacts of genome instability are clear, but how can genome instability confer an adaptive advantage to cells under environmental stress? A new study from NIEHS investigators addressing this question is published in the February issue of the journal Genetics. The findings suggest mechanisms that may be employed by cancer cells or pathogenic fungi on the path to drug resistance.

Covo and colleagues used a novel assay to study chromosome gain in yeast and measure properties that cannot be properly addressed with chromosome loss assays. (Photo courtesy of Steve McCaw)

The study, first published online in December 2013, found that defects in the sister chromatid cohesion (SCC) pathway led to chromosome instability, which allowed yeast to survive toxic environmental exposures. Shay Covo, Ph.D., is the corresponding author on the paper and a former postdoc in the NIEHS Laboratory of Molecular Genetics. He performed the work while in the Chromosome Stability Group led by Michael Resnick, Ph.D.

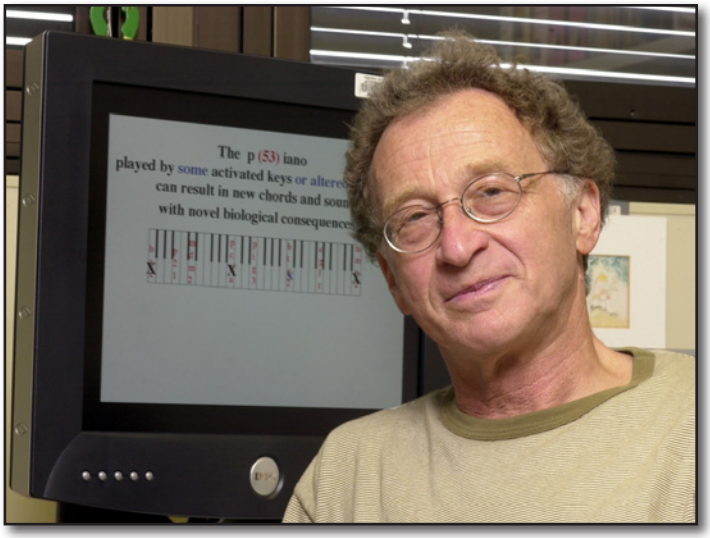
Addressing cancer using a simple model organism

Covo and his colleagues designed a novel assay to study the rate of aneuploidy, or the gain or loss of entire chromosomes, in different yeast strains in response to copper exposure. While previous work has addressed chromosome loss, this assay allowed the researchers to focus on chromosome gain and to identify the nature of the aneuploidy that arose. "We were the first to combine a quantitative measurement of the rate of chromosome gain within a population with a detailed analysis of the karyotype [a visual representation] of some of the isolates within the population," explained Covo.

Using the assay, the researchers found that single mutations in the SCC pathway could greatly affect genome instability, as determined in the lab of their collaborator, Lucas Argueso, Ph.D., at Colorado State University. They observed copper resistant mutants with surprisingly imbalanced genomes.

"We had an isolate in which the degree of aneuploidy was 33 percent of the entire genome," Covo said. "Such events are seen in cancer, but to observe them in a simple model system, after a short selection period, is impressive."

The study's model provides a great opportunity to explore carcinogenic mutations and genome instability in a tractable system. Defects in SCC are known to play a role in tumorigenesis. "These results may explain why similar types of mutations are so frequent in tumors and how the imbalanced genomes often seen in cancer can actually arise," said Covo. "One can now ask what genetic and environmental determinants play a role in such phenomenon."



Resnick's leadership encouraged the kind of open-ended inquiry that helped Covo flourish as a researcher during his training at NIEHS. (Photo courtesy of Steve McCaw)

The work also suggests a mechanism by which single-celled organisms can easily adapt to a stressful environment. As Covo pointed out, "Since the work was done in yeast, our results are even more relevant to diseases caused by other yeast such as *Candida albicans*. It is known that drug resistance among Candida species is associated with chromosome gain."

Since the completion of the yeast study, Covo has started his own lab in the Department of Plant Pathology and Microbiology at the Hebrew University of Jerusalem (see story). He is currently applying the rationale developed for his work at NIEHS to a more general agricultural system to study pesticide and fungicide resistance. Covo said that having his work highlighted by Genetics has increased interest and requests for reprints, which he hopes will lead to more chances for collaboration.

Citation: Covo S, Puccia CM, Argueso JL, Gordenin DA, Resnick MA. 2014. The sister chromatid cohesion pathway suppresses multiple chromosome gain and chromosome amplification. Genetics 196(2):373-384.

(Staton Wade, Ph.D., is an Intramural Research Training Award fellow in the NIEHS Chromatin and Gene Expression Group.)

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PEPH webinar highlights alternative testing methods

By Audrey Pinto

Promoting the discovery and application of novel test models for environmental health research is a core objective of the NIEHS strategic plan.

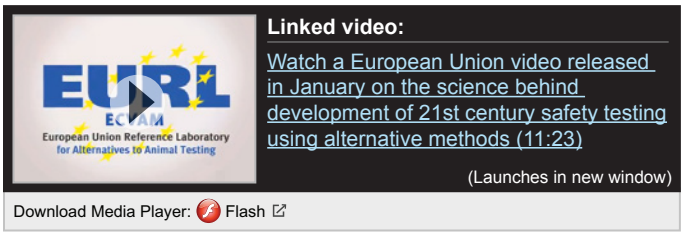
The NIEHS Partnerships for Environmental Public Health (PEPH) sponsored a webinar Jan. 23 highlighting the Institute's commitment to develop, apply, and validate cutting-edge scientific methods aimed at ensuring human and animal health, while protecting the environment. Efforts include in-house research by NIEHS and NTP scientists; collaborations with agency partners to advance predictive toxicology and alternative testing; and grant awards.

The two presenters – Elizabeth Maull, Ph.D., of the NTP Biomolecular Screening Branch, and Kristie Willett, Ph.D., an NIEHS-funded grantee with the Environmental Toxicology Research Program at the University of Mississippi School of Pharmacy — described their group's efforts to foster and promote scientifically sound alternative test methods.

Maull is an NTP toxicologist in the Biomolecular Screening Branch, the NTP lead group for Tox21, and a NICEATM administrator. (Photo courtesy of Steve McCaw)

Advancing, promoting, and validating the discovery of innovative test models

Maull introduced webinar attendees to the unique role the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) and the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) play in promoting the acceptance of innovative test methods by both the federal government and the global community.



Using what the groups call the 3Rs, Maull explained, "[The mission is to] facilitate interagency and international collaboration to promote the development, regulatory acceptance, and use of alternative tests that encourage the reduction, refinement, or replacement of animal test methods."

Maull pointed to Tox21, now beginning Phase III, as a successful partnership among four federal agencies — NIEHS/NTP, the National Center for Advancing Translational Sciences, the U.S. Environmental Protection Agency, and the U.S. Food and Drug Administration — to promote the emerging field of predictive toxicology. The consortium is using alternative methods including high-throughput screening assays — *in silico* models; lower-organism model systems, such as zebrafish and *Caenorhabditis elegans*; and investigating 3-D tissue models; as well as the so-called organs on a chip. The goal of this partnership is to evaluate and prioritize approximately 10,000 chemicals of toxicological concern.

While great strides have been made in the design and application of new testing models, Maull said, "There is an ongoing need for an evolving definition of 'validation' that should be responsive to new technologies and ongoing paradigm shifts in toxicity testing."

Willett is a professor of pharmacology with research interests that include using fish models to study mechanisms of polycyclic aromatic hydrocarbon toxicity. (Photo courtesy of Ole Miss Communications)

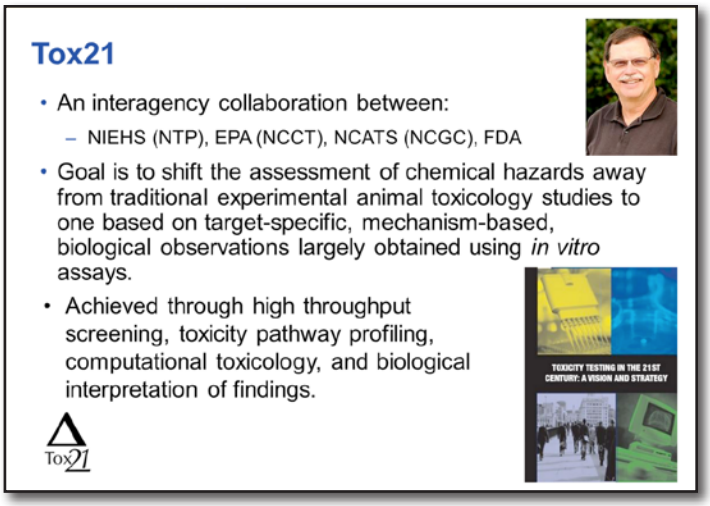
Zebrafish — a model organism for tracking the fetal origins of human diseases

Willett is a passionate proponent of the contribution and utility of research with zebrafish (*Danio rerio*) as a model organism. She opened her presentation by highlighting the advantages of using zebrafish for testing the effects of environmental toxicants. Willett pointed out that because scientists have extensive information on the genomic, developmental, and reproductive biology of zebrafish, they are invaluable to the global scientific community in providing answers to the origins and causes of human diseases, including cancer and neurological diseases.

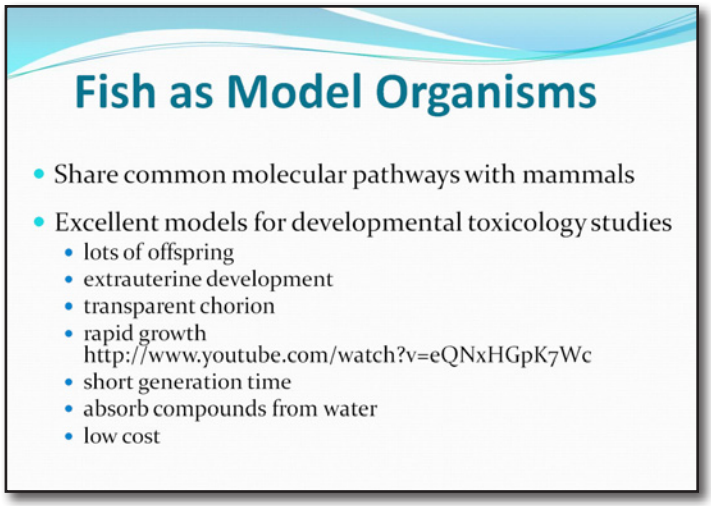
As she explained, "Not only do zebrafish share common molecular pathways and diseases with mammals, which make them ideal for developmental toxicological studies, they also possess a very unique characteristic — their extrauterine development is transparent, so that researchers can watch the progress of a disease from an environmental exposure while it's happening." To highlight this unique feature, Willett used her research findings on dietary benzo(*a*)pyrene exposure as a case study, to show the adverse developmental effects on body shape of multiple generations of offspring.

In summary, Willett said, "Because zebrafish produce large numbers of offspring that develop rapidly, researchers now have a test model that can evaluate the impact of toxicological exposures on multigenerational and transgenerational offspring in a matter of months instead of years."

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



With Tox21, the emphasis in toxicology is evolving from descriptions of pathological outcomes to prediction of the potential effects of chemicals on the biochemical pathways. (Slide courtesy of Elizabeth Maull)



As Willett explained, fish offer several important advantages over other animal models, including a 48-hour window of embryo development that parallels mammal development in a fraction of the time. (Slide courtesy of Kristine Willett)

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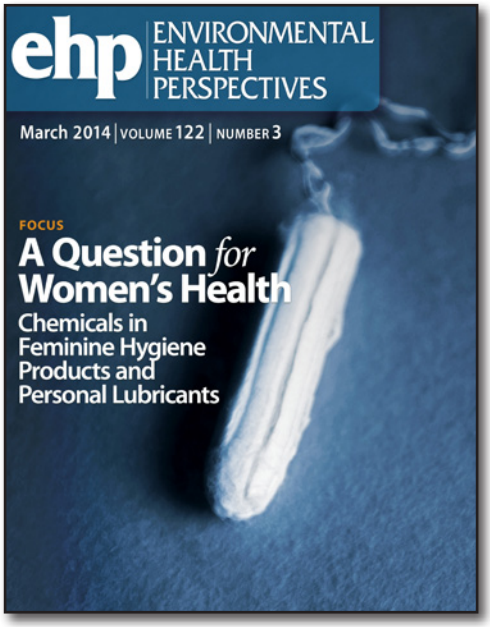
This month in EHP

http://twitter.com/ehponline

The March issue of Environmental Health Perspectives (EHP) focuses on the overlooked area of health impacts from feminine hygiene products and personal lubricants, as well as the new National Toxicology Program (NTP) Nonneoplastic Lesion Atlas.



Chemicals in Feminine Hygiene Products and Personal Lubricants

Mucous membranes in the vagina and vulva rapidly absorb chemicals without metabolizing them. But until recently, scant research existed on how chemicals in feminine hygiene products and personal lubricants may affect women's health. With recent findings emerging in this largely overlooked research area, several researchers and interest groups are calling for more research to fill in the data gaps.

NTP Nonneoplastic Lesion Atlas: A New Tool for Toxicologic Pathology

For decades, pathologists have diagnosed nonneoplastic lesions and other tissue findings by matching what they see under the microscope with a picture in a textbook or journal. A new website, hosted by NTP, is bringing that process into the digital age and promises to significantly improve the ability of researchers to evaluate noncancer findings in animal studies.

Featured research and related news articles this month include:

- **Assessing Exposure and Health Consequences of Chemicals in Drinking Water —** Chemical Contaminants in Drinking Water: Where Do We Go From Here?
- **White Light-Emitting Diodes (LEDs) at Domestic Lighting Levels and Retinal Injury in a Rat Model —** Hidden Blue Hazard? LED Lighting and Retinal Damage in Rats
- **Arsenic Exposure Perturbs the Gut Microbiome and Its Metabolic Profile in Mice: An Integrated Metagenomics and Metabolomics Analysis —** Clues to Arsenic's Toxicity: Microbiome Alterations in the Mouse Gut

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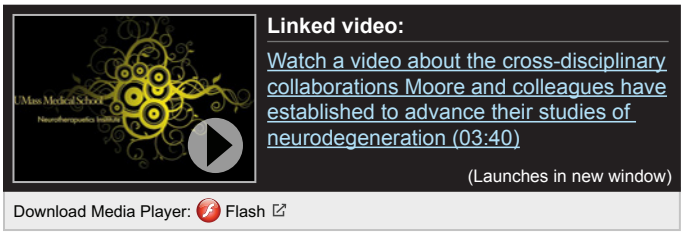
Distinguished Lecture Series to feature talk by Melissa Moore

By Suchandra Bhattacharjee

The next NIEHS distinguished lecture of 2014 will be presented by Melissa Moore, Ph.D., March 11, at 11:00 a.m., in Rodbell Auditorium. The talk on "Assembly and Dynamics of Uber Complex RNPs" is being hosted by Karen Adelman, Ph.D., head of the NIEHS Transcriptional Responses to the Environment Group.

Moore is the Eleanor Eustis Farrington Chair of Cancer Research, and co-director of both the RNA Therapeutics Institute (RTI) and the Neurotherapeutics Institute (NTI) at the University of Massachusetts (UMass) Medical School. She is also a Howard Hughes Medical Institute investigator. Moore was instrumental in starting Neurodegenerates, a group of faculty representing several disciplines that meets regularly to discuss and collaborate on neurodegeneration. The meetings led to the formation of the NTI.



The Moore laboratory at UMass focuses on eukaryotic RNA processing and metabolism. Her work involves posttranscriptional gene regulation in eukaryotes via mechanisms involving RNA, and centers on pre-mRNA processing and large RNA-protein (RNP) complexes to study their basic structures and functions, as well as their contributions to human disease.

Moore is sure to have good advice for the fellows who will join her for lunch during her visit to NIEHS. "I never started out to work on RNA, but that's where I've happily ended up," she is quoted as saying in her HHMI biography. "Sometimes when students talk to me, they seem to think they need to have their entire future planned out from the start. But they don't. I certainly didn't." (Photo courtesy of Melissa Moore)

Areas of investigation include single molecule analysis of spliceosome assembly; messenger RNP (mRNP) structure and function; RNP egress by nuclear envelope budding; and development of novel therapeutic approaches targeting RNA-based processes. Her research significantly spans the disciplines of cell and molecular biology, biochemistry, chemical biology, biophysics, and bioinformatics, for divergent insights into RNA metabolism.

As part of RTI, Moore is interested in understanding the molecular and cellular mechanisms of neurodegeneration, RNA metabolism, and local translation in neural degeneration, axon, and synapse loss after injury and in several diseases, including amyotrophic lateral sclerosis, Huntington's disease, Alzheimer's disease, Charcot-Marie-Tooth disease, Parkinson's disease, and traumatic brain injury.

Moore has published 95 peer-reviewed articles and reviews that are highly cited, and has presented invited lectures worldwide. Among her other accolades, Moore has been awarded the Searle Scholars Program Award, David and Lucile Packard Foundation Fellowship Award, Harcourt General Charitable Foundation New Investigator Award, and American Society for Biochemistry and Molecular Biology William C. Rose Award.

(Suchandra Bhattacharjee, Ph.D., is a special volunteer in the NIEHS Free Radical Metabolism Group)

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RTI to host NIH metabolomics symposium March 7

By Eddy Ball

RTI International will host the second NIH Eastern Regional Comprehensive Metabolomics Resource Core (RCMRC) Symposium March 7 at its headquarters in Research Triangle Park, N.C. Sponsored by RTI RCMRC and Bruker BioSpin, the event is free and open to the public.

Registration is required for the full-day symposium to be held in the RTI Dreyfus Auditorium, which includes a complimentary lunch.

The agenda features overviews of the RTI RCMRC by Director Susan Sumner, Ph.D., and program coordinator Jason Burgess, Ph.D., as well as presentations by Kim Colson, Ph.D., of Bruker BioSpin, and four academic scientists offering insights in metabolomics research and applications in nutritional analysis and drug development.

Speakers on the agenda include Elaine Holmes, Ph.D., of Imperial College London; Jeffrey MacDonald, Ph.D., of the University of North Carolina at Chapel Hill (UNC-CH); Martin Kohlmeier, M.D., Ph.D., of the UNC-CH Nutrition Research Institute; and Rima Kaddurah-Daouk, Ph.D., of Duke University.

In September 2012, Sumner and her team established RTI RCMRC as part of a $9.3 million grant from the NIH Common Fund. Like its five sister cores, the goals of RTI RCMRC are to establish national standards, increase the national capacity to provide metabolic profiling and data analysis, and facilitate institutional development of research, training, and outreach. The funding has supported a research core at RTI, an internship program, and collaborations with metabolomics training programs at UNC-CH and the University of Alabama at Birmingham.

In August 2013, the group held its first annual symposium, which was well attended by NIEHS scientists representing several disciplines and research interests (see story).

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Extramural papers of the month

By Nancy Lamontagne

- New animal model reveals role of abnormal DNA repair in lupus
- Developmental exposure to BPA increases prostate cancer risk
- Human stem cells reveal gene-environment interaction in Parkinson's disease
- Simulation helps prioritize housing interventions based on health outcomes and costs

Srp Superfund Research Program

Read the current Superfund Research Program Research Brief. New issues are published on the first Wednesday of each month.

New animal model reveals role of abnormal DNA repair in lupus

An NIEHS grantee and colleagues discovered that a genetic mutation involved in DNA repair leads to lupus in mice. Their new mouse model of lupus could provide insight into the environmental mechanisms of the disease and, potentially, other autoimmune diseases.

The lack of an animal model has hindered research of systemic lupus erythematosus (SLE), which causes widespread inflammation in internal organs, joints, and the nervous system. Genome-wide association studies have suggested that a mutation in the gene coding for DNA polymerase beta (Pol B) is involved in SLE. DNA Pol B is a key enzyme in the genome integrity process of base excision repair, which defends cells and organisms against direct insults to DNA.

To determine if decreased DNA Pol B activity results in SLE, the researchers genetically engineered mice to express lower amounts of the enzyme. The mutant mice developed lupus-like disease and shorter antibody heavy-chain junctions. They also showed dramatically increased levels of somatic hypermutation, a process by which the immune system adapts to new foreign elements. The researchers say their findings suggest that mutations in DNA repair genes, associated with immunological processes, could lead to the development of autoimmune disease, including SLE.

Citation: Senejani AG, Liu Y, Kidane D, Maher SE, Zeiss CJ, Park HJ, Kashgarian M, McNiff JM, Zelterman D, Bothwell AL, Sweasy JB. 2014. Mutation of POLB Causes Lupus in Mice. Cell Rep 6(1):1-8.

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Developmental exposure to BPA increases prostate cancer risk

NIEHS grantees report that exposure to bisphenol A (BPA) during development increases the risk for cancer in human prostate tissue. The researchers believe that BPA reprograms prostate stem cells to be more sensitive to estrogen throughout life, leading to increased susceptibility to diseases, including cancer.

To investigate the effect of BPA on human cells, the researchers implanted mice with epithelial stem-like cells cultured from prostates of young, disease-free men. Prostate stem cells arise during early fetal development and produce and maintain a man's prostate tissue throughout his life. To mimic exposure to BPA during embryonic development, the mice were fed 100 or 250 micrograms of BPA per kilogram body weight for two weeks following implantation, the time during which the cells produced humanized prostate tissue. The BPA fed to the mice was equivalent to levels ingested by the average person.

The researchers found that 33 to 36 percent of tissue samples taken from the mice fed BPA had either precancerous lesions or prostate cancer, compared to only 13 percent for a control group of mice. For mice that received prostate stem cells exposed to BPA before implantation, and then were continuously exposed to BPA as the stem cells produced prostate tissue, 45 percent of the tissue samples had precancerous lesions or cancer.

Citation: Prins GS, Hu WY, Shi GB, Hu DP, Majumdar S, Li G, Huang K, Nelles J, Ho SM, Walker CL, Kajdacsy-Balla A, van Breemen RB. 2014. Bisphenol A promotes human prostate stem-progenitor cell self-renewal and increases in vivo carcinogenesis in human prostate epithelium. Endocrinology; doi: http://dx.doi.org/10.1210/en.2013-1955 [Online 1 January 2014].

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Human stem cells reveal gene-environment interaction in Parkinson's disease

Researchers, supported in part by NIEHS, used human stem cells derived from Parkinson's disease patients to show that a gene mutation, combined with exposure to pesticides, produces free radicals in neurons, leading to nerve cell death. Prior to this work, the link between pesticides and Parkinson's disease was based mostly on animal studies and epidemiological research.

Parkinson's disease is characterized by loss of dopamine-containing neurons in the substantia nigra, a structure located in the midbrain that plays an important role in reward, addiction, and movement. Using the human stem cell model, researchers created two sets of dopamine-containing neurons that were genetically identical, except for an alpha-synuclein mutation in one set of neurons. The researchers exposed the cells to pesticides, including paraquat, maneb, and rotenone. In the cells with the mutation, they observed excessive free radicals, as well as damage to the dopamine-containing neurons, which led to cell death. The detrimental effects were observed even with short exposures to doses well below EPA-accepted levels.

The genetically matched neurons revealed that, in the cells with the mutation, exposure to pesticides disrupts a key mitochondrial pathway that normally protects dopamine-containing neurons. Using high-throughput screening, the researchers identified a molecule called isoxazole that protected mutant neurons from cell death induced by the tested pesticides. Since several FDA-approved drugs contain derivatives of isoxazole, these findings may have potential clinical implications for treating Parkinson's.

Citation: Ryan SD, Dolatabadi N, Chan SF, Zhang X, Akhtar MW, Parker J, Soldner F, Sunico CR, Nagar S, Talantova M, Lee B, Lopez K, Nutter A, Shan B, Molokanova E, Zhang Y, Han X, Nakamura T, Masliah E, Yates JR 3rd, Nakanishi N, Andreyev AY, Okamoto S, Jaenisch R, Ambasudhan R, Lipton SA. 2013. Isogenic human iPSC Parkinson's model shows nitrosative stress-induced dysfunction in MEF2-PGC1alpha transcription. Cell 155(6):1351-1364.

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Simulation helps prioritize housing interventions based on health outcomes and costs

An NIEHS grantee and colleagues used their pediatric asthma model to simulate the effects of environmental factors, medication compliance, seasonality, and medical history on indoor pollutant concentrations and asthma outcomes. The simulation provided information that can be used to prioritize individual and building interventions, based on how they affect health outcomes and costs.

The researchers applied their previously developed discrete event simulation model of pediatric asthma, to estimate the potential effect of multiple building interventions in low-income multifamily dwellings. They focused on comparing health care use with the estimated costs of implementing interventions. Interventions such as integrated pest management and repairing kitchen exhaust fans led to 7 to 12 percent reductions in serious asthma events, with payback periods of one to three years. Weatherization efforts aimed only at tightening the separation between the interior and the exterior environments of a building led to 20 percent more serious asthma events. However, combining this weatherization with repairing kitchen exhaust fans and eliminating indoor pollution sources mitigated this effect.

The researchers say that their findings increase physicians' understanding of the effect that home environmental changes have on asthma, thus bridging the gap between environmental health and clinical science.

Citation: Fabian MP, Adamkiewicz G, Stout NK, Sandel M, Levy JI. 2014. A simulation model of building intervention impacts on indoor environmental quality, pediatric asthma, and costs. J Allergy Clin Immunol. 2014 Jan. 133(1):77-84.

(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 Deacqunita Diggs, Gabriel Knudsen, Gwendolyn Louis, and Simone Otto

- SIRT1 plays a vital role in bile acid absorption and homeostasis
- X-ray crystallography reveals previously unknown damage response pathway
- Nicotine has a positive cognitive effect on hippocampal neurons
- Identifying respiratory syncytial virus using gene markers

SIRT1 plays a vital role in bile acid absorption and homeostasis

NIEHS researchers and collaborators discovered that Sirtuin 1 (SIRT1), a nicotinamide adenine dinucleotide-dependent protein deacetylase and key regulator of energy balance, is also important for bile acid homeostasis in the intestines. A dysregulation of bile acid homeostasis has been associated with liver damage and a host of other gastrointestinal and metabolic diseases.

Using a genetically modified, tissue-specific SIRT1 knockout mouse model, SIRT1 iKO, researchers found that SIRT1 deficiency in the intestines decreased the transport of bile acids across the ileum, by reducing the signaling of the hepatocyte nuclear factor 1alpha/farnesoid X receptor pathway. These mice also displayed reduced absorption of intestinal bile, increased liver bile acid synthesis, and decreased liver accumulation of bile acids. SIRT1 iKO mice on a high bile acid diet were partially protected from developing liver damage.

The authors suggest that therapeutics that specifically target intestinal SIRT1 could be developed to treat bile acid-related diseases, such as cholestasis, a condition in which the flow of bile from the liver to the duodenum, the first part of the small intestine, is slowed or blocked. **(GL)**

Citation: Kazgan N, Metukuri MR, Purushotham A, Lu J, Rao A, Lee S, Pratt-Hyatt M, Lickteig A, Csanaky IL, Zhao Y, Dawson PA, Li X. 2013. Intestine-specific deletion of SIRT1 in mice impairs DCoH2-HNF-1alpha-FXR signaling and alters systemic bile acid homeostasis. Gastroenterology; doi:10.1053/j.gastro.2013.12.029 [Online 31 December 2013].

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X-ray crystallography reveals previously unknown damage response pathway

Lesions that result from the insertion of RNA into DNA are removed by the protein aprataxin, according to researchers at NIEHS. The scientists named the process RNA-DNA damage response and believe it is responsible for removing many potentially harmful DNA lesions. Mutations in aprataxin, however, impair efficient processing of RNA-DNA damage. The inability to remove RNA-DNA lesions may contribute to ataxia with oculomotor apraxia 1 (AOA1), a heritable cerebellar-wasting condition, as well as other neurodegenerative diseases linked to APTX mutations.

The researchers studied aprataxin and RNA-DNA interactions using X-ray crystallography, coupled to biochemistry and genetics, in yeast. They crystallized human aprataxin mutants in complex with RNA-DNA substrates, to visualize the aprataxin lesion processing reaction in high resolution. They determined that one of the AOA1 linked aprataxin mutations, which differed from the wild-type by only a single amino acid, distorts the RNA-DNA damage recognition pocket in the protein and blocks its ability to efficiently recognize and process RNA-DNA lesions.

This work helped to establish and expand the hypothesis that progressive neurological diseases, such as AOA1, may in part be due to repeated incorporation of ribonucleotides into genomic DNA over many years in quiescent neurons. Aprataxin gene mutations are critical in heritable AOA1-type neurological diseases, and understanding these molecular mechanisms may aid in new therapies for neurological diseases and certain types of cancer. **(GK)**

Citation: Tumbale P, Williams JS, Schellenberg MJ, Kunkel TA, Williams RS. 2014. Aprataxin resolves adenylated RNA-DNA junctions to maintain genome integrity. Nature 506(7486):111-115. [Story]

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Nicotine has a positive cognitive effect on hippocampal neurons

NIEHS researchers have elucidated the cellular mechanism by which nicotine has a positive cognitive effect in hippocampal neurons, according to a study in the Journal of Neuroscience. The work provides a basis for novel therapeutics for combatting cognitive impairment in disorders such as schizophrenia and Alzheimer's disease.

Specifically studying the synaptic connection between dentate granule cells and the pyramidal cells of the CA3 region of the hippocampus, scientists discovered that activation of presynaptic, but not postsynaptic, alpha7 nicotinic acetylcholine receptors enhances the current in the postsynaptic cell. Scientists used biosensors to confirm the importance of presynaptic activity. Stimulation of presynaptic nicotinic receptors increased the level of calcium generated by action potentials, which, in turn, increased the likelihood of neurotransmitter release onto CA3 pyramidal cells. This stimulation resulted in an increase of the amplitude of the excitatory postsynaptic current. Since the effects of this stimulation persisted for several minutes, they further demonstrated it was accomplished through a mechanism involving the calcium-dependent signaling molecule protein kinase A (PKA).

The connection between dentate granule cells and CA3 neurons controls the neuronal output of the hippocampus. Determining the mechanism by which nicotinic receptors modulate this output improves the understanding of how nicotine affects hippocampal-dependent learning and memory. **(SO)**

Citation: Cheng Q, Yakel JL. 2014. Presynaptic alpha7 nicotinic acetylcholine receptors enhance hippocampal mossy fiber glutamatergic transmission via PKA activation. J Neurosci 34(1):124-133.

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Identifying respiratory syncytial virus using gene markers

NIEHS researchers and collaborators have developed a cell model to investigate genes involved in respiratory syncytial virus (RSV) infection, which is common in infants and children. The model identified candidate genes, and one viral gene in particular, that may be used as a biomarker to validate RSV infections.

Using RSV, the authors infected human lymphoblastoid cell lines (LCLs) from several ethnic groups, including Northern European, African American, and Japanese. They found that RSV infectivity differed among individuals, as well as between the ethnic groups.

In addition, they utilized LCL microarray gene expression data from HapMap, an international project sponsored by the National Human Genome Research Institute to develop a map of human haplotypes, or genes, that are inherited together, to determine patterns of human DNA variation. Out of the 62 genes that correlated with RSV infection, they found that slight sequence changes, or polymorphisms, in the gene for influenza myxovirus resistance 1 (MX1) were associated with increased expression of RSV in LCLs, and with an increased risk of severe RSV disease in an Argentinian infant cohort. The data suggest MX1 is a susceptibility marker for RSV infection, and the authors' translational approach may be used to predict other genes that confer RSV risk. **(DD)**

Citation: Ciencewicki JM, Wang X, Marzec J, Serra ME, Bell DA, Polack FP, Kleeberger SR. 2014. A genetic model of differential susceptibility to human respiratory syncytial virus (RSV) infection. FASEB J; doi:10.1096/fj.13-239855 [Online 13 January 2014].

(Deacqunita L. Diggs, Ph.D., is a National Health and Environmental Effects Laboratory (NHEERL) fellow in the EPA Developmental Toxicity Branch. Gabriel Knudsen, Ph.D., is a Cancer Research Training Award (CRTA) fellow in the NCI Center for Cancer Research Laboratory of Toxicology and Toxicokinetics. Gwendolyn Louis is an Oak Ridge Institute for Science and Education (ORISE) research fellow in the EPA Reproductive Toxicology Division. Simone Otto is an Intramural Research Training Award (IRTA) fellow in the NIEHS Ion Channel Physiology Group.)

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Inside the Institute

NIEHS awards ceremony honors 2013 achievements

By Allison Eason

NIEHS staff gathered to give their colleagues well-deserved recognition at the Feb. 11 annual awards ceremony in Rodbell Auditorium. The event was hosted by NIEHS and NTP Director Linda Birnbaum, Ph.D., and emceed by Stavros Garantziotis, M.D., medical director of the NIEHS Clinical Research Unit and head of the Matrix Biology Group in the Laboratory of Respiratory Biology.

Birnbaum welcomed the audience with a message to both employees and contractors. "From a budget and planning standpoint, I don't remember a year with more challenges," she said. "But, even when the craziness resulted in a government shutdown, you were unshaken and remained committed to our mission."

Garantziotis kept the audience entertained, as he introduced the awardees.

Cynthia Radford, center, a 14-year veteran of NIEHS, accepts an Unsung Hero Award for her outstanding coordination of the NIEHS Training Program, from Birnbaum, left, and Joellen Austin, NIEHS associate director for management. (Photo courtesy Steve McCaw)

NIEHS Awardees

Unsung Hero Awards: Beth Bowden, Shannon Duncan, Essie Jones, Jacqueline Locklear, Molly Puente, Cynthia Radford

Peer Recognition Awards: Gary Bird, Jennifer Collins, Mitzie Walker

Individual Merit Awards: Joel Abramowitz, Michelle Campbell, Mary Grant, Patrick Mastin, Sheila Newton

Divisional Group Merit Awards

Division of the National Toxicology Program: Patrick Barbour, Veronica Robinson, Bradley Collins, Suramya Waidyanatha

Office of Management: Rhonda Carroll, Rob Levine, Ron Faison, Mike Merrick, Jack Field, Anthony Patterson, John Grovenstein, Roy Reter, Sharon Hite, Mike Tyson, Robin Jones, Vernee Wilson, Ed Kang, Ellen Moul, Dona McNeill

Shannon Duncan, center, accepts an Unsung Hero Award for exemplary integrity, efficiency, and professionalism in administering the Laboratory of Structural Biology office, from Birnbaum, left, and Darryl Zeldin, M.D., NIEHS scientific director . (Photo courtesy of Steve McCaw)

Division of Extramural Research and Training: Kathy Ahlmark, Ted Outwater, Sharon Beard, Jim Remington, Pamela Clark, Jonathan Rosen, Donald Ellis, Deborah Weinstock, Chip Hughes

Office of the Director: Rebecca Boyles, Stephanie Holmgren, Allen Dearry

Cross Divisional Group Merit Awards

For the design and implementation of a high-functioning Inventory Management System: Vernee Morgan, April Parker, Andrea Glass, Sharon Hite, Kecia Jacobs, Robert Lockett, Kelly Powell, Nancy Powell, Frances Primm, Kent Stone, Amanda Weaver, Kenneth Webb

For exemplary teamwork and successful creation of the NIEHS responsive website for mobile devices: Beth Bowden, Joseph Poccia, Cheryl Thompson, Sharon Hite

For the development of the first NIEHS Scholars Connect Program boot camp that supports the next generation of environmental health scientists: Aleksandra Adomas, Miranda Bernhardt, Elena Braithwaite, Qing Cheng, Jackson Hoffman, Huei-Chen Lao, Sabrina Robertson, Misty Thomas, Joy Winuthayanon

2013 NIEHS Highlights

- 15-year anniversary of the NIEHS/EPA Children's Environmental Health and Disease Prevention Research Centers (see story).
- Publication of the Interagency Breast Cancer and Environmental Research Coordinating Committee report, Breast Cancer and the Environment: Prioritizing Prevention (see story).
- NIEHS Clinical Research Unit partnered with NIEHS labs to begin new studies, including the study on BPA exposure from cash register receipts.
- NIEHS obtained division status for the National Toxicology Program (NTP).
- A court decision supported the NTP listing of styrene in the Report on Carcinogens.
- NIEHS completed the implementation planning for the 2012-2017 Strategic Plan.
- The Scholars Connect Program continues to introduce local college students to the Institute and to a career in environmental health research.

For exemplary engagement and participation in the Data Science and Information Technology Working Group: Perry Blackshear, Cindy Lawler, Rebecca Boyles, Leping Li, Matthew Burr, Claire Long, Pierre Bushel, Kent Stone, David Fargo, Paul Wade, Stavros Garantziotis, Mitch Williams, Michelle Hooth, Leroy Worth, Chip Hughes

For exemplary leadership of interdivisional planning teams in support of the NIEHS Strategic Plan: Janice Allen, Frederick Miller, Trevor Archer, Heather Nicholas, John Balbus, Daniel Shaughnessy, David Balshaw, Claudia Thompson, Allen Dearry, Raymond Tice, Christine Flowers, Frederick Tyson, Christopher Long, Michael Waalkes, Scott Masten, Paul Wade

For outstanding participation and service to the Interagency Breast Cancer and Environmental Research Coordinating Committee: Gwen Collman, Ed Kang, Jennifer Collins, Kate Ryan, Suzanne Fenton, Dale Sandler, Christine Flowers

For leadership and facilitation of the DERT reorganization: Ellen Moul, Angela Sanders, Nicole Popovich

Fellows' Awards for Research Excellence (FARE)

Christopher Campos, Senthilkumar Cinghu, Huaixin Dang, Neal Englert, Bret Freudenthal, George Fromm Jr., Bonnie Joubert, Mahita Kadmiel, Nevzat Kazgan, YuanYuan Li, Kristin Lichti-Kaiser, Ngome Makia, Stela Palii, Sabrina Robertson, Lindsay Smith, Erica Ungewitter, Qingshan Wang, Jeremy Weaver, Gary ZeRuth

Following the ceremony, employees enjoyed refreshments in the cafeteria and celebrated with their colleagues, friends, and family.

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

The Property Recovery team poses with Birnbaum, left, and Austin, right, as they receive a Merit Award for the coordination and accounting of more than 500 information technology components, allowing for a successful contractor transition. (Photo courtesy of Steve McCaw)

Strategic Plan implementation team leaders pose with Birnbaum, left, as they accept their Merit Award. (Photo courtesy of Steve McCaw)

2013 Fellows Award for Research Excellence (FARE) winners each received a $1,000 stipened to attend a scientific meeting of their choice, to present their research. (Photo courtesy of Steve McCaw)

Birnbaum, left, and Zeldin, right, pose with Mary Grant, V.M.D., center, as she receives a Merit Award for her selfless dedication to the NIEHS mission and stellar leadership as interim branch chief of the Comparative Medicine Branch. (Photo courtesy of Steve McCaw)

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