

January 2015

NIEHS Spotlight



[HP2020 progress report webinar features Birnbaum](#)

NIEHS and National Toxicology Program Director Linda Birnbaum, Ph.D., was one of two scientific experts featured on a Dec. 5 Healthy People 2020 webinar.



[NIEHS leads disaster research response project](#)

Aubrey Miller, M.D., shared details of the new project, dubbed DR2, at the 2014 Worker Safety and Health Technical Conference this fall in Washington, D.C.



[ONES awardee honored by Society of Toxicology](#)

Vishal Vaidya, Ph.D., will receive the 2015 Achievement Award from the Society of Toxicology in recognition of his significant early-career contributions to toxicology.



[London delivers prestigious Harvard lecture](#)

Stephanie London, M.D., Dr.P.H., returned Nov. 19 to her academic home at the Harvard School of Public Health to deliver the 17th annual James L. Whittenberger lecture.

Clinical Feature



[NIEHS needs military volunteers to study muscle disease](#)

NIEHS researchers are recruiting active duty military personnel to study risk factors for myositis — regardless of whether they have the disease.

Science Notebook



[2014 Papers of the year](#)

From more than 2836 NIEHS-funded studies published in 2014, leaders of the institute selected 23 for special recognition as Papers of the Year.



[The impacts of air pollution on the immune system](#)

In her Dec. 16 distinguished lecture, clinician and immunologist Kari Nadeau, Ph.D., discussed the effects of air pollution on human immune function.



[NIEHS scientists determine how environment contributes to several human diseases](#)

The study, published in Nature, found that DNA polymerase can insert into the DNA strand molecules that have been damaged by environmental exposures.

NIEHS Spotlight



[Eight current and former NIEHS grantees elected 2014 AAAS fellows](#) 🏆

Among the 401 new fellows of the American Association for the Advancement of Science are eight outstanding scientists who have been funded by NIEHS.



[Zeldin honored with NICHD Partnership Award](#) 🏆

NIEHS Scientific Director Darryl Zeldin, M.D., was recognized Dec. 3 by the Eunice Kennedy Shriver National Institute of Child Health and Human Development.



[EPA pesticide panel considers new approach for chemical screening](#)

NTP scientists were on hand Dec. 2–5 to support a high-throughput proposal for screening and prioritizing chemicals in the Endocrine Disruptor Screening Program.



[NIEHS visits classrooms of STaRS teachers](#)

NIEHS followed the successful Science, Teachers, and Research Summer Institute with co-teaching visits to participants' classrooms.

Science Notebook



[Woodruff explores the next generation of tissue chip development](#)

According to Teresa Woodruff, Ph.D., *in vitro* predictive toxicology is poised to take the next big step in modeling, from single-dimension to multi-dimension integrated tissue cultures.



[Triclosan promotes liver tumor growth in mice, say SRP researchers](#) 🏆

Triclosan promotes liver tumors in mice and should be studied further in humans, say NIEHS-funded researchers at two Superfund Research Programs.



[NTP advisors like what they hear at meeting](#)

The National Toxicology Program Board of Scientific Counselors was pleased with program updates presented at their Dec. 9-10 meeting.



[Linking inflammation with environmental exposures](#)

The NIEHS inflammation faculty featured NTP efforts to uncover links between environmental exposures and inflammation in a Dec. 11 webcast seminar.



[Plant breeding models could aid toxicological research](#)

Russell Wolfinger, Ph.D., director of scientific discovery and genomics at SAS Institute, discussed genomic selection models in a data science seminar.



[Papers of note — cadmium, phthalates, and PAHs](#)

New studies by NIEHS grantees examine cadmium, phthalates, and polycyclic aromatic hydrocarbons and effects on human health.

Inside the Institute



[The good, the bad, and the ugly of the blood-brain barrier](#)

The popular Big Picture, Small Talk series continued with David Miller, Ph.D., and additional speakers are lined up for 2015.



[Volunteers from NIEHS wrap up outreach module at middle school](#)

Now entering its third year, the NIEHS Citizen Schools outreach program completed its latest module Dec. 11 at Lowes Grove Middle School in Durham, North Carolina.



[NIEHS celebrates commitment to excellence](#) 🏆

NIEHS celebrated staff achievements at the Dec. 12 annual awards ceremony.

Science Notebook



[This month in EHP](#)

The January issue of Environmental Health Perspectives looks at challenges of maintaining hygiene during emergencies and setting a limit for arsenic in rice.



[Perera to discuss maternal exposures to the fetus in distinguished lecture](#) ▶ Video

The NIEHS Distinguished Lecture Series will feature a talk Jan. 13 by grantee Frederica Perera, Dr.P.H., Ph.D., of Columbia University.

Extramural Research

[Extramural papers of the month](#)

- [Triclosan associated with liver damage in mice](#)
- [Potential treatment for Parkinson's targets mitochondrial dysfunction](#)
- [Biomonitoring studies should include phosphate flame retardants](#)
- [Killifish used to find genes that allow environmental adaptation](#)

Intramural Research

[Intramural papers of the month](#)

- [NTP finds a better animal model to evaluate the effects of chemical exposure](#)
- [Time-lapse crystallography reveals link between oxidative stress and disease](#)
- [MED25 mediates epigenetic regulation of human drug metabolism gene CYP2C9](#)
- [Researchers find protein involved in glucocorticoid-resistant asthma](#)
- [Ambient air pollution increases the risk of asthma and wheeze in adult women](#)

Calendar of Upcoming Events

- **Jan. 6**, in the Executive Conference Room, noon-1:00 p.m. — Receptor Mechanisms Discussion Group, featuring Masahiko Negishi, Ph.D., discussing “Biology of the Conserved Phosphorylation of Nuclear CAR, ER alpha, and FXR”
- **Jan. 13**, in Rodbell Auditorium, 11:00 a.m.-noon — Distinguished Lecture Series presentation on “The Fetal Window of Susceptibility: Using Molecular Epidemiology to Understand the Role of Prenatal Environmental Exposures on Child Health and Development,” by Frederica Perera, Dr.P.H., Ph.D.
- **Jan. 14-15**, in Rodbell Auditorium, 8:30 a.m.-5:00 p.m. — NIEHS Exposome Workshop
- **Jan. 20**, in Keystone 1003AB, 1:00-2:00 p.m. — Big Picture, Small Talk: Elk River Spill, by Scott Auerbach, Ph.D.
- **Jan. 23**, in Rodbell Auditorium, 8:00 a.m.-4:30 p.m. — Cross-divisional Minisymposium on Epigenetics
- **Jan. 27**, in Rall D350, 11:00 a.m.-noon — National Toxicology Program Laboratory Seminar Series presentation on “Brain Slice Models for CNS Drug Discovery: Tales of Natural and Unnatural Products,” by Donald Lo, Ph.D.
- **Jan. 27**, webinar, 1:00-3:00 p.m. — Interagency Coordinating Committee on the Validation of Alternative Methods Community of Practice Webinar, with John Wambaugh, Ph.D., and Barbara Wetmore, Ph.D., discussing “Reverse Toxicokinetics: Using *In Vitro* Data to Estimate Exposures That Could Be Associated With Adverse Effects *In Vivo*,” [register](#)
- **Jan. 29**, in Rodbell Auditorium, 1:00-2:00 p.m. — NIEHS Office of the Director seminar with Manijeh Berenji, M.D., discussing “Environmental Exposures and Impact on Reproductive Health: Current Knowledge and Future Directions”
- View More Events: [NIEHS Public Calendar](#)

NIEHS Spotlight

HP2020 progress report webinar features Birnbaum

By Eddy Ball

NIEHS and National Toxicology Program Director Linda Birnbaum, Ph.D., was one of two scientific experts featured during a Dec. 5 [Healthy People 2020 \(HP2020\)](#) webinar focused on environmental health and tobacco use. She presented an overview of NIEHS programs and new environmental health research findings related to leading health indicators.

Birnbaum was joined by Tim McAfee, M.D., director of the Centers for Disease Control and Prevention (CDC) Office on Smoking and Health. The community highlight section of the program featured Kara Skahen, director of the Live Smoke Free program at the Association for Nonsmokers-Minnesota, where translation of research has led to a 30-fold increase in the number of smoke-free public housing units from 2007 to 2014.



As she discussed the effects of environmental exposures on children's development, Birnbaum emphasized the role of primary prevention. "A good start lasts a lifetime," she told the audience. (Photo courtesy of Steve McCaw)

Linked video:
Tune into the webinar (01:27:38)
[Note: requires appropriate software to load](#)
(Launches in new window)

Download Media Player: Windows Media [↗](#)

“We spend about 30 percent of our budget on prevention,” Birnbaum proudly said of the role of NIEHS research support on improving public health. “In many ways, we are the public health institute at NIH.”

For his part, McAfee pointed to effective measures to reduce tobacco consumption and related adverse health effects. Use of tobacco products is now less than half the rate in 1965. “We know what works,” he said.

A bumpy road to HP2020 targets

While there is reason for optimism, Birnbaum and other experts on the program emphasized that much remains to be done before HP2020 can meet all of its leading health indicator targets. As an introductory overview by Karen DeSalvo, M.D., acting assistant secretary for health at the U.S. Department of Health and Human Services, made it clear that cigarettes are still the leading cause of preventable death in the U.S., and millions of deaths each year continue to be attributable to preventable environmental causes.

Following DeSalvo was Irma Arispe, Ph.D., associate director of the CDC National Center for Health Statistics. Out of 64 HP2020 measurable [environmental health objectives](#), only 18 have been met or are improving, she said. In terms of the 66 HP2020 measurable [tobacco use objectives](#), 28 have been met or are improving, while 27 show little or no detectable change.

On the environmental front, research of the kind Birnbaum described is uncovering the adverse health effects of much lower levels of exposure to arsenic, manganese, lead, and mercury, as well as endocrine-disrupting chemicals found in plastics and fire retardants. New research on the developmental origins of health and disease, and growing awareness of health disparities, have complicated the environmental picture, by adding concerns that, in some cases, go beyond the HP2020 agenda.

In many ways, the path to meeting tobacco use targets is clearer, although the barriers are significant. McAfee pointed to the 18-fold funding advantage enjoyed by tobacco marketers and important gaps in regulation. Only a small part of tobacco tax and lawsuit settlement resources are actually being spent on the cessation campaign, and there is a troubling rise in the use of unregulated e-cigarettes, deceptive advertising continues, and some populations continue to have high rates of use.

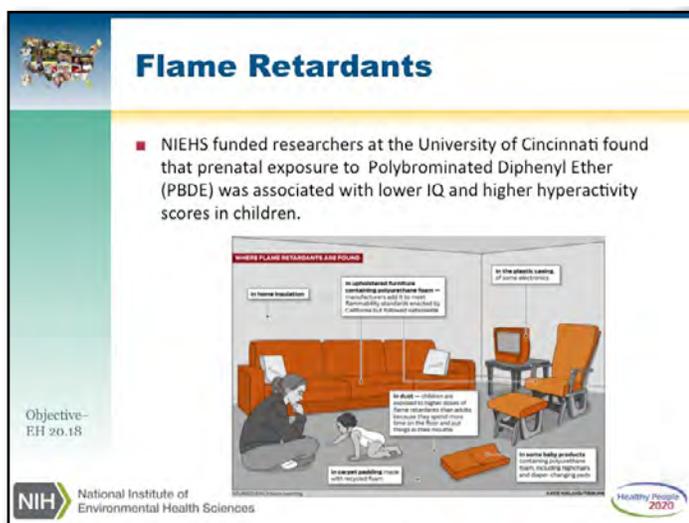
The final 30 minutes of the webinar featured a roundtable discussion, with presenters and representatives of partner agencies answering questions from viewers.

NIEHS and the interagency collaboration

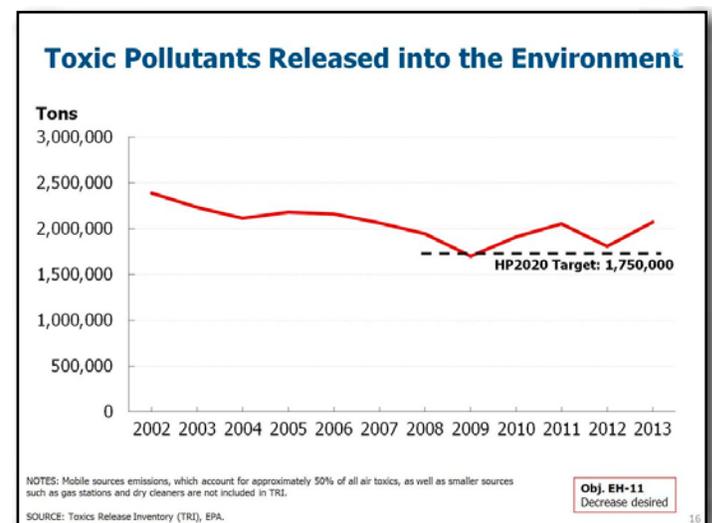
A federal interagency workgroup leads the HP2020 effort. It includes representatives from U.S. Department of Health and Human Services agencies and offices, as well as 8 other agencies and departments with primary concerns ranging from justice and education to housing and transportation.

NIEHS takes part in the HP 2020 initiative as the co-lead agency on the [environmental health](#) topic area, and is one of three National Institutes of Health agencies leading the [respiratory diseases](#) topic area. The NIEHS HP2020 representative is program analyst Bill Jirles of the Office of Policy, Planning, and Evaluation.

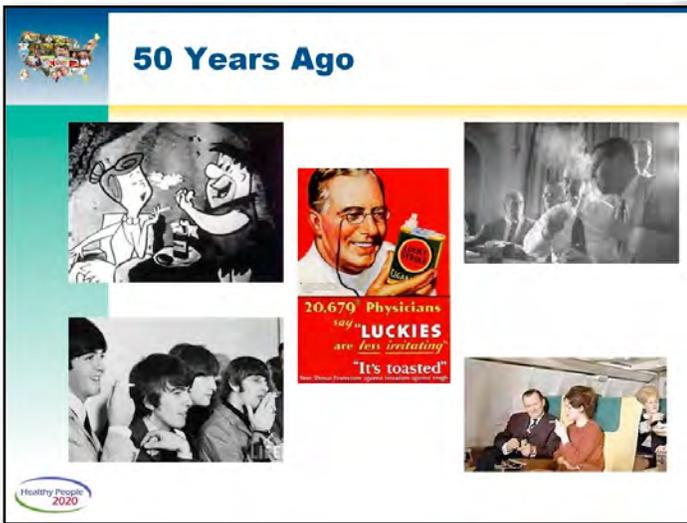
Presentations and additional information related to the more than 35 webinars in the 2010-2014 HP2020 series are available [online](#). The series continues in February 2015 with a progress review of objectives in the areas of social determinants of health, and lesbian, gay, bisexual, and transgender health.



Exposure to fire retardant chemicals, as illustrated in this slide from Birnbaum's presentation, is still nearly 50 percent greater than targeted by EH 20.18. (Image courtesy of Linda Birnbaum and HP2020)



This slide from Arispe's presentation illustrates bumps on the road to reducing the amount of toxic pollutants released each year. Newly introduced chemicals, and better understanding of the effects of exposures at low levels and during windows of susceptibility, are almost constantly complicating environmental health metrics. (Image courtesy of Irma Arispe and HP2020)



McAfee showed this slide as a reminder of how much the smoking picture has improved over the past 50 years. In the 1950s and 1960s, smoking was allowed nearly everywhere, as celebrities and even cartoon figures glamorized the habit, and physicians went on record as recommending brands. (Image courtesy of Tim McAfee and HP2020)

[Return to Table of Contents](#)



What Makes for a Good Policy?

- Written in a lease or house rules.
- Defines "smoke free" and what areas of the property are covered.
- Consequences for violations are clearly defined; violations may result in eviction.
- No grandfathering.
- 100% of indoors are covered (outdoor areas are a plus!)

Skahen described resources available from the Live Smoke Free program. They include clear guidelines, educational resources, signage, a how-to module, a statewide smoke-free housing directory, training and technical assistance, and an online webinar series. (Image courtesy of Kara Skahen and HP2020)

NIEHS leads disaster research response project

By Eddy Ball

NIEHS Senior Medical Advisor [Aubrey Miller, M.D.](#), shared details of a new National Institutes of Health NIH Disaster Research Response Project, dubbed DR2, at the 2014 Worker Safety and Health Technical Conference this fall in Washington, D.C.

The event was organized and hosted by the National Response Team (NRT), a consortium of 15 federal departments and agencies with interests in disaster response. The DR2 presentations included a discussion of disaster training and exercises led by NIEHS Worker Education and Training Director [Chip Hughes](#).

“Getting health researchers on-site immediately following a disaster is a must for collecting the samples and data we need to help understand any impacts on people’s health and to be able to improve our responses to prevent illness and injuries in the future,” Miller told the audience. “Disaster response research requires science on steroids to get critical information in a timely way.”

Following the conference, NIEHS and National Toxicology Program Director Linda Birnbaum, Ph.D., received a letter of thanks from NRT co-chairs Denise Matthews, a safety and occupational health specialist for the Occupational Safety and Health Administration, and Brian Kovak, an environmental scientist with the U.S. Environmental Protection Agency (EPA).



Miller leads disaster response for the NIEHS Office of the Director. He previously served a similar role with EPA. (Photo courtesy of Steve McCaw)

“It is vital to improve responders’ and managers’ ability to recognize risk and stress indicators and utilize improved interventions and protective actions,” wrote Matthews and Kovak. “This research will certainly advance worker safety and health.”

The DR2 project

In conjunction with the institute’s NIH partner, the National Library of Medicine (NLM), Miller, Hughes, and NIEHS Clinical Research Branch Acting Director [Stavros Garantziotis, M.D.](#), along with other NIEHS staff from various programs, are leading the DR2 effort to be better prepared for performing timely disaster research well before weather, terroristic attacks, and other disruptive events strike. They are working to develop quick access to useful data collection tools, rapid development and implementation of research protocols, a national environmental health researcher network, and capacity to deploy trained researchers to the field.

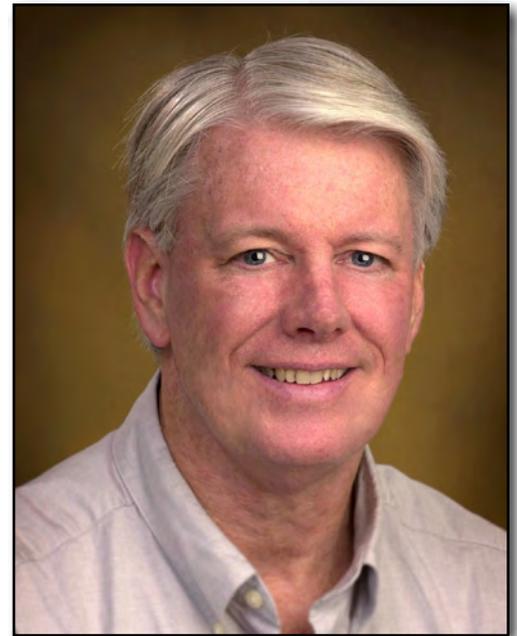
In his discussion of the importance of timely disaster research, Miller referred to several events that occurred over the past 15 years, including the World Trade Center terrorist attack, Hurricane Katrina, the Deepwater Horizon oil spill, the Elk River, West Virginia chemical oil spill, and the recent Ebola response. He posed the questions that people typically want to know about each of the events — “Is it safe for communities and workers? Did our approaches to reduce harm or health impacts work? How can we better prepare for the next one?”

Since August 2013, the NIEHS and NLM team has been helping to define and achieve DR2 objectives (see graphic). A key concept of the effort includes collaboration among government agencies, across the environmental health sciences community, and among stakeholders.

The goal of DR2 is the creation of a readily accessible infrastructure that will allow researchers to look beyond the immediate devastation of disasters and understand ways to improve responses and help protect people.

According to Miller, the DR2 efforts will serve to help all researchers, regardless of the nature of the event, by helping to build needed infrastructure and processes for the collection of invaluable information. He said he hopes it will soon save scientists on the ground the precious time often lost in reinventing tools and protocols; ushering them through the lengthy approval process; and training responders and data professionals.

As part of its role as DR2 organizer and lead, NIEHS has set up a dedicated email address at DR2@niehs.nih.gov for questions and comments.



Hughes oversees grants for training workers in disaster response and postevent remediation. Several recent grantee workshops included disaster response exercises. (Photo courtesy of Steve McCaw)

DR2 milestones

- Readily available health data collection tools
 - Data repository
 - Public DR2 [webpage](#)
 - NIEHS disaster response protocol
- Disaster research response network
 - Coordinated broad spectrum of parties interested in improving response capabilities and responding to environmental emergencies
 - Set up ways to engage communities in research response and facilitate citizen science
- Workshops, training materials, and guidance
 - Conducted a [training exercise](#) in Los Angeles to test DR2 tools and strategies
 - Co-sponsored [Enabling Public Health Research During Disasters workshop](#)
 - Supported planning Ebola response [workshop](#)

NIH National Institute of Environmental Health Sciences
Your Environment. Your Health.

Gulf Oil Spill, April 2010

Media Room | Directory | Meetings and Events | Member Login

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES
Advising the Nation. Improving Health.

ABOUT THE IOM | REPORTS | ACTIVITIES

Explore by Topic: [] Keyword Search: []

Browse History

Sign up for E-mail Updates: [] RSS: [] Text Size: []

ACTIVITY

Assessing the Human Health Effects of the Gulf of Mexico Oil Spill
6/17/2010

Decades later, we still can feel the consequences of the Exxon Valdez oil spill. How will the even larger crisis in the Gulf impact our health? The IOM will hold a meeting June 22-23 to discuss the health issues for those living and working near the Gulf.

Read More >



IOM Workshop, New Orleans. June 22-23, 2010

Key Points

- Longitudinal human health research is clearly indicated
- Health studies should begin as soon as possible
- Mental health & psychosocial impacts must not be overlooked
- Sensitive populations need to be monitored
- External stakeholders must be part of the process
- Data and data systems should be developed to support wider research efforts

This slide from Miller's talk underscores important components of disaster response research in the aftermath of the Deepwater Horizon oil spill. With DR2, these components should be identified before the event, not in a workshop two months afterwards.

NIH National Institute of Environmental Health Sciences
Your Environment. Your Health.

NIH Disaster Research Response (DR2) Project

Project Started Aug. 2013 and is ongoing

Pilot project to help galvanize and accelerate needed infrastructure as part of a larger HHS Effort

Objectives

1. Central repository data collection tools & research protocols
2. NLM public website: "Disaster Research Responders"
3. **Rapid Data Collection Capability:** baseline epi., clinical, & biospecimens
4. **Environmental Health Research Response Network (EHS Network)**
5. **Training** intra/extramural disaster researchers
6. **Share & Integrate:** HHS/federal response & recovery frameworks
7. **Toxicology Support: information and testing (new)**
8. **Environmental Data: to go with human health information (new)**

In this slide, Miller pointed to the broad objectives of an integrated response strategy.

ONES awardee honored by Society of Toxicology

By Eddy Ball

NIEHS grantee Vishal Vaidya, Ph.D., will receive the 2015 Achievement Award from the Society of Toxicology (SOT), in recognition of his significant early-career contributions to the field.

The [award](#) consists of a plaque and a \$2,000 cash stipend to be presented at the SOT Annual Meeting Awards Ceremony March 22, 2015, in San Diego. It recognizes outstanding toxicologists who are fewer than 15 years into their careers since completing their highest awarded degree.

“Your selection as the 2015 Achievement Award recipient is a well-deserved honor in recognition of your significant achievements,” wrote chair of the SOT Awards Committee Barbara Beck, Ph.D., in her Oct. 28 letter of congratulations.

Outstanding New Environmental Scientist (ONES) awardee

A specialist in kidney biology and systems toxicology, [Vaidya](#) has faculty appointments at Brigham and Women’s Hospital in Boston, where he directs the Laboratory of Kidney Toxicology and Regeneration; at Harvard Medical School, where he heads the Systems Toxicology Program within the Harvard Program in Therapeutic Sciences; at Harvard School of Public Health, where he directs the 5-credit graduate level course Principles of Toxicology-Molecular and Translational Toxicology every fall; and at the Harvard Clinical and Translational Science Center, where every spring he directs the course Understanding Biomarker Science: From Molecules to Images.

His laboratory uses cellular systems, mouse models, and human biospecimens, and applies methodologies at the interface of cell and molecular biology, systems pharmacology, and translational science in understanding kidney disease.

In recognition of his early-career potential, Vaidya received a 5-year ONES award in 2012, joining six other young researchers who shared approximately \$4 million in grant awards made that year (see [story](#)). Prior to his ONES award, Vaidya was the recipient of an NIH Pathway to Independence Award, from NIEHS, in 2009 (see [story](#)).

Vaidya was also a summer intern at NIEHS during graduate school. He completed postdoctoral training in the renal division of Brigham and Women’s Hospital, supported by a grant from the National Kidney Foundation in 2005, prior to his faculty appointments at Harvard.



NIEHS supports Vaidya’s research on fibrinogen signaling in kidney tissue repair. (Photo courtesy of Vishal Vaidya)



Honoring toxicology's best and brightest

In addition to his SOT Achievement Award, one of the society's highest honors, Vaidya was selected for the SOT American Scientist of Indian Origin Young Investigator Award in 2012 and the Leading Edge in Basic Science Award in 2014. In 2013, he was one of just six scientists to receive the coveted Burroughs Wellcome Fund Innovation in Regulatory Science Award, which provides up to \$500,000 over five years to support innovative research in regulatory science (see [story](#)).

SOT has presented the Achievement Award nearly every year since 1967. Vaidya joins a number of other outstanding young scientists with NIEHS ties who have received the award, including former NTP toxicologist Michael Waalkes, Ph.D.; 2006 ONES awardee Donna Zhang, Ph.D.; and veteran grantees Kenneth Ramos, M.D., Ph.D.; Martin Philbert, Ph.D.; Ivan Rusyn, M.D., Ph.D.; and Gary Miller, Ph.D.

[Return to Table of Contents](#)

Also honored by SOT

- University of Arizona research associate [John Clarke, Ph.D.](#), with a 2015 Best Postdoctoral Publication Award for NIEHS-funded research — [Clarke JD](#), [Hardwick RN](#), [Lake AD](#), [Lickteig AJ](#), [Goedken MJ](#), [Klaassen CD](#), [Cherrington NJ](#). 2014. Synergistic interaction between genetics and disease on pravastatin disposition. *J Hepatol* 61(1):139-47.
- Professor and member of the NIEHS-funded Superfund Research Program at Duke University [Theodore Slotkin, Ph.D.](#), with the 2015 SOT Education Award
- Professor Emeritus [Gunter Oberdorster, D.V.M., Ph.D.](#), of the University Rochester's NIEHS-funded Ph.D. program in toxicology, with the 2015 SOT Merit Award

London delivers prestigious Harvard lecture

By Ernie Hood

NIEHS researcher Stephanie London, M.D., Dr.P.H., has shown that Thomas Wolfe was wrong — you can, in fact, go home again — as she returned Nov. 19 to her academic home at the Harvard School of Public Health to deliver the 17th annual James L. Whittenberger lecture.

London received her bachelor's, master's, doctorate, and medical degrees from Harvard. So it was entirely appropriate that [London](#), deputy chief of the NIEHS Epidemiology Branch and head of the Genetics, Environment, and Respiratory Disease Group, was selected to give the keynote [address](#) at the symposium.

The annual event honors the memory of James L. Whittenberger, M.D., who was the founder and director of the Harvard NIEHS Center for Environmental Health, and chair of the Department of Physiology at the Harvard School of Public Health for 32 years. The symposium and lecture were named in his honor in 1983.

London's lecture, "Smoking and the Epigenome Across the Lifecourse," summarized one aspect of her group's [research](#), which revealed epigenetic processes that may underlie a connection between maternal smoking and several adverse health

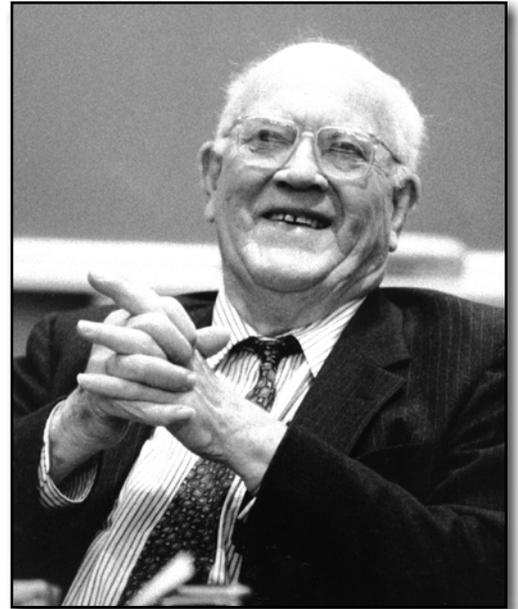


London's research group focuses on genetics and the environment in relation to respiratory endpoints, including asthma, pulmonary function, and chronic obstructive pulmonary disease. (Photo courtesy of Steve McCaw)

effects among children of smoking mothers, such as low birth weight, some childhood cancers, impaired lung function, and early respiratory illnesses.

A distinguished legacy

The roster of past Whittenberger Symposium [speakers](#) reads like a who's who of environmental health sciences, including NIEHS directors and several prominent NIEHS grantees, such as Philip Landrigan, M.D., from the Icahn School of Medicine at Mount Sinai (2009), Caroline Tanner, M.D., Ph.D., from the University of California, San Francisco (2012), former NIEHS Director David Schwartz, M.D., now at the University of Colorado School of Medicine (2007), and current Director of NIEHS and the National Toxicology Program Linda Birnbaum, Ph.D., who presented the [lecture](#) in 2010.



A pioneering expert in a multidisciplinary approach to environmental health, Whittenberger served the Harvard School of Public Health for 36 years, until his retirement in 1982. (Photo courtesy of Harvard University)

London was welcomed and introduced by Douglas Dockery, Sc.D., chair of the Department of Environmental Health at the Harvard School of Public Health, and director of the Harvard NIEHS Center for Environmental Health.

“The opportunity to give the Whittenberger Lecture was a dream come true,” said London. “My years of experience and education at Harvard have shaped my whole scientific career, so it was both humbling and uplifting to return there and share some of what I’ve learned with my Harvard colleagues and their students.”

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

[Return to Table of Contents](#)

Eight current and former NIEHS grantees elected 2014 AAAS fellows

By Eddie Ball

Among the 401 new fellows announced Nov. 24 by the American Association for the Advancement of Science (AAAS) are eight outstanding scientists whose work has been funded by NIEHS.



ADVANCING SCIENCE, SERVING SOCIETY

Four are currently funded, and another four enjoyed NIEHS support in previous years. The newly elected fellows are being honored by their peers for their contributions to innovation, education, and scientific leadership. They were honored by the Section on Biological Sciences, the Section on Pharmaceutical Sciences, and the Section on Medical Sciences.

“The accomplishments of the new Fellows will be celebrated at the 2015 AAAS Annual Meeting, convening this year under the theme ‘Innovations, Information, and Imaging,’” the AAAS press release stated. The new Fellows will be presented with an official certificate and a gold rosette pin Feb. 14 at the AAAS Fellows Forum in San Jose, California.

Current grantees and their projects

- [Marisa Bartolomei, Ph.D.](#), of the University of Pennsylvania — Transgenerational Effects of Endocrine Disruptors: Epigenetics and Physiology
- [Trey Ideker, Ph.D.](#), of the University of California, San Diego — A Systems Approach to Mapping the DNA Damage Response
- [Franklin Pugh, Ph.D.](#), of Pennsylvania State University, University Park — Promoter Regulation in Response to Environmental Stress
- [Barry Rosen, Ph.D.](#), of Florida International University — The Human Arsenic Methylation Pathway

Previously funded grantees and their projects

- [Joanna Floros, Ph.D.](#), of the Pennsylvania State University Hershey Medical Center — Ozone Effects on Function of Surfactant Protein Variants
- [Stephen Hecht, Ph.D.](#), of the University of Minnesota — DNA Adducts of the Carcinogen Acetaldehyde
- [Karen Vasquez, Ph.D.](#), of the University of Texas at Austin — Comparative Mechanisms of Genomic Instability
- [Jan Vijg, Ph.D.](#), of Albert Einstein College of Medicine — Direct Somatic Mutation Analysis Through Sequencing

AAAS is the world's largest general scientific society and publishes the journal *Science*. Founded in 1848, the society includes more than 261 affiliated societies and academies of science, serving about 10 million individuals. A nonprofit organization, the society is open to all, and fulfills its mission to advance science and serve society through initiatives in science policy, international programs, and science education.

[Return to Table of Contents](#)

Zeldin honored with NICHD Partnership Award

By Eddy Ball

NIEHS Scientific Director Darryl Zeldin, M.D., received a Partnership Award Dec. 3 from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD).

Presented by NICHD Director Alan Guttmacher, M.D., during a ceremony at the Lipsett Amphitheater on the National Institutes of Health (NIH) campus in Bethesda, Maryland, the award is a tribute to Zeldin's willingness to reach across NIH to help colleagues at other institutes and centers.

Over the past year, Zeldin provided support as NICHD reorganized its Intramural Research Program (IRP) under the direction of NICHD Scientific Director Constantine Stratakis, M.D., D.Med.Sc.



During a reception at the NIH Clinical Center following the award ceremony, Zeldin joined NICHD colleagues for refreshments. Shown from left are Stratakis, Zeldin, NICHD Deputy Director Catherine Spong, M.D., and Guttmacher. (Photo courtesy of NICHD)

“Dr. Zeldin shared his experience with how staff all worked together at NIEHS to implement needed changes,” Stratakis said. “His advice was essential in how we moved along with our own changes and reorganization in response to a Blue Ribbon Panel review of our own program.”

According to Stratakis, Zeldin helped NICHD leaders respond more quickly and efficiently to the challenges of reorganization. “There are many levels of what is going on at NICHD IRP where Dr. Zeldin contributed with advice and by sharing his experiences. But, as just one example of his help, the metrics presented by him became the basis for a system proposed by NICHD investigators for assessing scientific productivity,” Stratakis said.

[Return to Table of Contents](#)

EPA pesticide panel considers new approach for chemical screening

By Catherine Sprankle

National Toxicology Program (NTP) scientists joined colleagues from the U.S. Environmental Protection Agency (EPA) at an advisory panel meeting to present a high-throughput approach for screening and prioritizing chemicals in EPA’s Endocrine Disruptor Screening Program.

The Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel, made up of experts from government and academia, met Dec. 2-5 to consider the proposed approach, which has the potential to be more efficient and robust than current practices.

Finding alternatives to animal testing

Federal agencies work to reduce the use of animals in research and testing. Methods that use fewer or no animals, or that reduce animal pain and distress, are referred to as **alternative methods**. NICEATM supports NTP high-throughput screening projects and conducts other projects relevant to test method development. NICEATM includes contract staff employed by ILS.

Tests identify chemicals that interfere with hormones

The Endocrine Disruptor Screening Program was established to identify substances found in pesticides and other chemical products that could interfere with the normal function of hormones and potentially cause health problems in humans and wildlife.

The panel focused on an approach to identifying substances that could interfere with estrogen and androgen hormone pathways, which are mostly associated with female and male sex characteristics. Current approaches to identifying these substances use data from animal tests, but the proposed approach uses data from automated cell- and biochemical-based *in vitro* methods.

Knowledge and technology underlie new approach

Warren Casey, Ph.D., director of the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), presented the Center’s comparison of animal test data and high-throughput screening data for substances that could mimic the action of estrogen hormones. The key question to consider, he noted, was whether animal tests used to identify potential estrogen-active substances still added value to the screening program.

“A lot has happened in recent years to make *in vitro* methods more useful and informative; technologies and data handling methods have improved, and a better understanding of mammalian physiology has been applied to making better assays,” Casey explained.

Nicole Kleinstreuer, Ph.D., a member of the Center’s Integrated Laboratory Systems, Inc. (ILS) contract support staff, followed with an analysis of data on substances that could mimic the action of androgen hormones. Other scientists from the EPA National Center for Computational Toxicology and the EPA Office of Science Coordination and Policy gave presentations on interpretation and application of the *in vitro* data, approaches to estimating exposure, and interpretation and application of the exposure data.

The panel was impressed by the work that went into the testing and analysis, and members of industry and animal welfare groups expressed their enthusiasm for the approach being proposed by the EPA.

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

[Return to Table of Contents](#)

NIEHS visits classrooms of STaRS teachers

By Kelly Lenox

Two participants in the successful Science, Teachers, and Research Summer (STaRS) Institute received classroom visits from NIEHS staff, most recently in December. During the two-week [program](#) for teachers in July, Huei-Chen Lao, of the NIEHS Office of Science Education and Diversity, offered to follow up with a co-teaching opportunity, to support the teachers as they shared with their students the knowledge and experiences they gained in the program.

Nash-Rocky Mount Early College High School

Lao traveled Oct. 10 with trainee Eric Milliman, Ph.D., and biologist Kevin Trotter, both of the Epigenetics and Stem Cell Biology Laboratory, to Brandi Simonof’s sophomore biology class at Nash-Rocky Mount Early College High School. They taught students about population genetics and polymerase chain reactions. In addition, Milliman and Trotter brought equipment and materials so students could carry out polymerase chain reactions on cheek swabs, to test for the presence of a certain DNA sequence.



Joining colleagues from EPA, Casey made a point about advances in automated screening while introducing his presentation to the advisory panel. (Photo courtesy Nicole Kleinstreuer)



Petrovich was actively involved in the summer program at NIEHS, shown above instructing teachers prior to a lab session. (Photo courtesy of Steve McCaw)

“We brought a project that would introduce a new concept to the students and provide good hands-on experience,” said Lao. Conveniently, the time required for the reactions to run provided an opportunity for students to grill the visitors about careers in science, the specifics of their jobs, and what types of training are necessary. “This is a more rural environment, so they don’t see a lot of scientists from day to day,” said Lao. “They were really curious about what the work is like.”

Lao emphasized to the students that an institute like NIEHS needs people with many different skills, from laboratory instrument maintenance, to animal care, to bench research. “We need people with all different talents, who can work together to get the job done,” she told the students.

Athens Drive High School, Raleigh

Travis Seese, who teaches Advance Placement biology at Athens Drive High School in Raleigh, North Carolina, also requested a co-teaching experience. On Dec. 10, Bob Petrovich, Ph.D., head of the NIEHS Protein Expression Core Laboratory, came along with Lao and led the research experience.

Again, the students were full of questions on topics such as personalized medicine and genetically modified organisms. But most of all, they were interested in how to prepare for a career in science. “How do you know when you know enough to be a scientist?” a student asked. “We never know enough,” Petrovich answered. “That’s why we never stop learning, and we collaborate with others when needed.”

In addition to education and training, Lao emphasized the ability to give and receive critique as central to the collaborative nature of state-of-the-art research.

“I think the best part was the exposure to people who do science on a daily basis,” said Lao. Students also expressed interest in the NIEHS summer internship program, which provides an opportunity gain practical experience.

Lao is planning additional co-teaching engagements in the coming year, and the STARS Institute will run again in the summer of 2015.



Trotter helped set up NIEHS equipment for students to use during the class. (Photo courtesy of Huei-Chen Lao)



Milliman guided a student as she prepared her sample for the polymerase chain reaction experiment. (Photo courtesy of Huei-Chen Lao)



*Standing, from left, Milliman, Simonof, and Lao provided a highly interactive experience for Simonof's biology students.
(Photo courtesy of Huei-Chen Lao)*

[*Return to Table of Contents*](#)

Clinical Feature

NIEHS needs military volunteers to study muscle disease

By Robin Arnette

Researchers suspect that genetics combines with environmental exposures to promote the development of an autoimmune disease called myositis, a rare disorder that causes muscle weakness (see sidebar). NIEHS scientists have initiated a [clinical study](#) that is examining the environmental risk factors for myositis in the military, due to a high incidence rate.

Preliminary studies suggest that over the past decade, military personnel developed myositis at a rate that was double that of nonmilitary personnel. Physicians have also documented large fluctuations from year to year in the number of service members being diagnosed with myositis.

“Although a few environmental exposures have been associated with myositis in civilians, to my knowledge, this study is the first to assess myositis development in active duty military personnel,” said Frederick Miller, M.D., Ph.D., deputy chief of the NIEHS Clinical Research Program and head of the Environmental Autoimmunity Group. “We need many more service people to join the study, so I urge military members, both with and without myositis, to sign up.”

Men and women may enroll at the National Institutes of Health [Clinical Center](#) in Bethesda, Maryland, the NIEHS [Clinical Research Unit](#) in Research Triangle Park, North Carolina, or through their physician’s office. The study has the following eligibility requirements:

- Healthy individuals or those diagnosed with myositis during military service
- Active, reserve, and inactive duty personnel
- Able to give consent, complete questionnaires, and donate blood

Individuals that meet the criteria should contact Komal Patel at (301) 443-6053 or komal.patel@nih.gov. Please refer to the study using the ClinicalTrials.gov identifying number: NCT01734369.

Study uses several approaches

[Miller](#) and his research team use three different approaches to discern the origins of myositis in military members. In one, they search military databases for information on medications, vaccines,

Myositis symptoms

Myositis patients experience weakness, difficulty breathing and swallowing, and skin rashes. All of these manifestations are the result of the body’s immune cells attacking the patient’s tissue.

Myositis, also known as idiopathic inflammatory myopathy, exists in three different forms: polymyositis, dermatomyositis, which includes a skin rash, and inclusion body myositis, which occurs in older individuals and involves distal muscles, or muscles furthest from the trunk.



Rider, like Miller, is a commissioned officer in the United States Public Health Service. (Photo courtesy of the National Institutes of Health)

infections, deployment locations, and other environmental exposure clues. In another, they compare the results of clinical visits of those who have myositis with healthy personnel, matched for age, gender, and ethnicity. The third method examines DNA methylation profiles in the blood and muscle of myositis and non-myositis participants.

Lisa Rider, M.D., deputy chief of the NIEHS Environmental Autoimmunity Group, has been involved in the military myositis study since it began in 2012. She said that there is a good chance the team will find at least one of the factors that lead to the increased risk of myositis in service members.

“In 2013, we published [work](#) that uncovered a link between short-term exposure to ultraviolet light and the development of myositis in children,” Rider said. “I suspect our military study will yield additional environmental factors to watch out for.”

[Return to Table of Contents](#)



Based in Bethesda, Maryland, Miller's research group studies the mechanisms for the development of autoimmune diseases. (Photo courtesy of Steve McCaw)

Science Notebook

2014 Papers of the year

Research funded by grants (click title for summary)

- [AhR controls endotoxin tolerance pathway](#)
- [Transcription factor influences codon choice and protein evolution](#)
- [Human stem cells reveal gene-environment interaction in Parkinson's disease](#)
- [New tool for assessing ovarian cancer](#)
- [Repairing UV-induced DNA damage](#)
- [One strain of bioremediation bacteria uses novel metabolic pathway](#)
- [Endoplasmic reticulum stress triggers obesity-driven liver cancer](#)
- [Phthalate exposure linked to preterm birth](#)
- [Girls are reaching puberty earlier](#)
- [Developmental exposure to BPA increases prostate cancer risk](#)

In-house research (click title for summary)

- [tssRNAs associated with paused Pol II serve as scaffold for transcription factors](#)
- [X-ray crystallography reveals previously unknown damage response pathway](#)
- [Human obesity increases colon cancer risk](#)
- [INO80 regulates embryonic stem cell fate and blastocyst development](#)
- [GWAS meta-analysis reveals new DNA loci of lung function](#)
- [Humans with APOE4 gene more prone to inflammation](#)
- [Control of histone expression by phosphorylation of an mRNA processing protein](#)
- [Histone-fold domain protein NF-Y promotes chromatin accessibility for cell specification](#)
- [SIRT1 regulates retinoic acid signaling and stem cell differentiation](#)
- [Maternal smoking linked to altered DNA in newborns](#)
- [Duking it out? My CA2 made me do it](#)
- [DNA replication errors in yeast offer new insight into cancer research](#)

National Toxicology Program research (click title for summary)

- [NTP finds a better animal model to evaluate the effects of chemical exposure](#)
- [NTP research finds low doses of inorganic arsenic cause lung tumors in male mice](#)
- [NTP review framework addresses environmental health questions](#)

Research funded by grants

AhR controls endotoxin tolerance pathway

Research by an NIEHS grantee and colleagues revealed new details regarding the mechanisms involved in endotoxin tolerance, a phenomenon in which prior exposure to endotoxin from gram-negative bacteria reduces the host's inflammatory response to subsequent exposure. The findings could lead to new approaches for treating infectious diseases, by controlling host-pathogen interactions.

The researchers used genetically modified mice to investigate the biological pathways involved in endotoxin tolerance. They found that primary exposure of mice to lipopolysaccharide activated the aryl hydrocarbon receptor (AhR) transcription factor and the liver enzyme tryptophan 2,3-dioxygenase. However, when the mice were again exposed to lipopolysaccharide, AhR engaged in long-term regulation of systemic inflammation only when indoleamine 2,3-dioxygenase 1 was present. The resulting endotoxin tolerance protected the mice against immune response damage to both gram-negative and gram-positive infections.

Citation: Bessede A, Gargaro M, Pallotta MT, Matino D, Servillo G, Brunacci C, Biccato S, Mazza EM, Macchiarulo A, Vacca C, Iannitti R, Tissi L, Volpi C, Belladonna ML, Orabona C, Bianchi R, Lanz TV, Platten M, Della Fazia MA, Piobbico D, Zelante T, Funakoshi H, Nakamura T, Gilot D, Denison MS, Guillemin GJ, DuHadaway JB, Prendergast GC, Metz R, Geffard M, Boon L, Pirro M, Iorio A, Veyret B, Romani L, Grohmann U, Fallarino F, Puccetti P. 2014. Aryl hydrocarbon receptor control of a disease tolerance defence pathway. *Nature* 511(7508):184-190. [[Synopsis](#)]

[Return to Table of Contents](#) | [Return to Papers of the Year](#)

Transcription factor influences codon choice and protein evolution

Research, partially supported by an NIEHS grant funded by the National Institutes of Health Common Fund, revealed that complex genomes simultaneously code for amino acids and regulatory information. The work adds a transcription factor binding code to the spectrum of other regulatory codes that are believed to influence protein evolution by influencing codon choice.

Scientists created a nucleotide resolution map showing where protein-coding regions of the human genome were occupied by a transcription factor. They looked at 81 diverse cell types, and found that approximately 15 percent of human codons simultaneously specify both proteins and transcription factor recognition sites. These dual-use codons, or duons, are highly conserved. They also found that more than 17 percent of single-nucleotide variants within duons directly altered transcription factor binding. The researchers concluded that widespread dual encoding of amino acid and regulatory information may be a fundamental feature of genome evolution.

Citation: Stergachis AB, Haugen E, Shafer A, Fu W, Vernot B, Reynolds A, Raubitschek A, Ziegler S, LeProust EM, Akey JM, Stamatoyannopoulos JA. 2013. Exonic transcription factor binding directs codon choice and affects protein evolution. *Science* 342(6164):1367-1372. [[Synopsis](#)]

[Return to Table of Contents](#) | [Return to Papers of the Year](#)

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

Researchers 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.

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.

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. \[Synopsis\]](#)

[Return to Table of Contents](#) | [Return to Papers of the Year](#)

New tool for assessing ovarian cancer

An NIEHS grantee and colleagues developed a new technique that may help predict ovarian cancer treatment response, cancer recurrence, and disease-free survival earlier and more effectively than current methods.

For many types of cancer, counting the number of tumor-attacking immune cells (TILs) that have migrated into the tumor offers a way to predict a patient's survival. The number of TILs indicates the body's immune response to cancer. The researchers developed a new approach called QuanTILfy, which uses droplet digital polymerase chain reaction technology to count TILs reliably, quickly, and cheaply.

The researchers tested QuanTILfy on tumor samples from 30 ovarian cancer patients who had survival times ranging from one to 22 months. The results showed an association between higher TIL counts and improved survival among women with ovarian cancer.

Citation: [Robins HS, Ericson NG, Guenthoer J, O'Briant KC, Tewari M, Drescher CW, Bielas JH. 2013. Digital genomic quantification of tumor-infiltrating lymphocytes. Sci Transl Med 5\(214\):214ra169. \[Synopsis\]](#)

[Return to Table of Contents](#) | [Return to Papers of the Year](#)

Repairing UV-induced DNA damage

An NIEHS grantee and colleagues report new details on how cellular machinery detects and signals for repair DNA damage caused by ultraviolet (UV) light.

When DNA is damaged by UV light, a protein called human UV-damaged DNA-binding protein (UV-DDB) recognizes this damage and signals for repair. Experiments revealed that UV-DDB stops along the DNA strand and transiently attaches to it. If it comes to a spot damaged by UV radiation, two molecules of UV-DDB converge and stay bound to the site, signaling DNA repair machinery.

The researchers also examined a UV-DDB with a mutation associated with xeroderma pigmentosum, an inherited disease where the body is unable to sufficiently repair damage caused by UV light. The mutant UV-DDB could still bind to DNA, but continued to slide along the DNA, rather than remaining at the damaged site to signal for repair.

Citation: Ghodke H, Wang H, Hsieh CL, Woldemeskel S, Watkins SC, Ropic-Otrin V, Van Houten B. 2014. Single-molecule analysis reveals human UV-damaged DNA-binding protein (UV-DDB) dimerizes on DNA via multiple kinetic intermediates. *Proc Natl Acad Sci U S A* 111(18):E1862-E1871. [[Synopsis](#)]

[Return to Table of Contents](#) | [Return to Papers of the Year](#)

One strain of bioremediation bacteria uses novel metabolic pathway

One strain of the organohalide-respiring bacterium, *Dehalococcoides mccartyi*, utilizes a novel strategy for generating compounds used in the bioremediation of chlorinated solvents, according to NIEHS grantees and their colleagues.

Anaerobes depend on the acetyl-CoA Wood-Ljungdahl pathway, which couples folate-mediated one-carbon metabolism to either carbon dioxide reduction or acetate oxidation through acetyl CoA to produce methyltetrahydrofolate (CH₃-THF) for methionine biosynthesis. However, *D. mccartyi* strain 195 lacks several Wood-Ljungdahl pathway enzymes, but still produces CH₃-THF by cleaving acetyl-CoA. Since this cleavage leads to a buildup of carbon monoxide (CO) and inhibits the growth of *D. mccartyi*, other anaerobes that metabolize CO coexist with the bacteria, thereby demonstrating an unusual syntrophic association. The authors also found that the pathway incorporates exogenous formate to support serine biosynthesis.

Citation: Zhuang WQ, Yi S, Bill M, Brisson VL, Feng X, Men Y, Conrad ME, Tang YJ, Alvarez-Cohen L. 2014. Incomplete Wood-Ljungdahl pathway facilitates one-carbon metabolism in organohalide-respiring *Dehalococcoides mccartyi*. *Proc Natl Acad Sci U S A* 111(17):6419-6424.

[Return to Table of Contents](#) | [Return to Papers of the Year](#)

Endoplasmic reticulum stress triggers obesity-driven liver cancer

Research that was partially funded by NIEHS has determined that activation of endoplasmic reticulum (ER) stress signaling is instrumental in the development of nonalcoholic steatohepatitis (NASH), a disease caused by inflammation and fat accumulation in the liver. NASH is also a risk factor in hepatocellular carcinoma, or liver cancer.

The ER is a network of membranous tubes that move proteins throughout a eukaryotic cell. Previous research implicated the ER in NASH, so the authors fed a high-fat diet to both wild type mice and major urinary protein-urokinase plasminogen activator (MUP-uPA) transgenic mice. They noted that the MUP-uPA mice exhibited greater liver damage, immune infiltration, and increased production of fatty acids, all hallmarks of NASH. The researchers determined that in light of this stress on the ER, a proinflammatory protein produced by macrophages, known as tumor necrosis factor, spurs the development of liver cancer.

Citation: Nakagawa H, Umemura A, Taniguchi K, Font-Burgada J, Dhar D, Ogata H, Zhong Z, Valasek MA, Seki E, Hidalgo J, Koike K, Kaufman RJ, Karin M. 2014. ER stress cooperates with hypernutrition to trigger TNF-dependent spontaneous HCC development. *Cancer Cell* 26(3):331-343.

[Return to Table of Contents](#) | [Return to Papers of the Year](#)

Phthalate exposure linked to preterm birth

NIEHS-supported research has found that, depending on the phthalate examined, women with the highest levels of exposure during pregnancy had 2-5 times the odds of preterm birth, compared to women with the lowest exposure. The findings point to phthalate exposure as a potentially preventable contributing factor to premature birth.

Using urine samples in a nested case control study design, the researchers examined associations between average levels of phthalate exposure during pregnancy and preterm birth in 130 mothers who had delivered prior to 37 weeks of completed gestation. The study also included 352 control mothers who delivered at or after 37 weeks.

They found that preterm birth showed the strongest dose-dependent associations with maternal levels of two di-2-ethylhexyl phthalate (DEHP) metabolites — mono-(2-ethyl)-hexyl phthalate and mono-(2-ethyl-5-carboxypentyl) phthalate — and the summed levels of all the DEHP metabolites.

Citation: Ferguson KK, McElrath TF, Meeker JD. 2014. Environmental phthalate exposure and preterm birth. *JAMA Pediatr* 168(1):61-67. [[Synopsis](#)] [[Story](#)]

[Return to Table of Contents](#) | [Return to Papers of the Year](#)

Girls are reaching puberty earlier

In a study of more than 1,200 girls that was part of the NIEHS Breast Cancer and the Environment Research Program, scientists found that breast development is occurring at an earlier age, and that earlier development is strongly associated with greater body mass index (BMI).

Girls were 6-8 years old when enrolled in the study and were followed from 2004 to 2011. At regular intervals, staff used Tanner staging to assess sexual maturity. They found that the age at onset of breast development, or stage 2, varied by ethnicity, BMI at baseline, and geographical site. For African-American, Hispanic, white non-Hispanic, and Asian participants, the median age at onset of breast stage 2 was 8.8, 9.3, 9.7, and 9.7 years, respectively. Girls with BMIs greater than the 85th percentile reached breast stage 2 at younger ages.

Citation: Biro FM, Greenspan LC, Galvez MP, Pinney SM, Teitelbaum S, Windham GC, Deardorff J, Herrick RL, Succop PA, Hiatt RA, Kushi LH, Wolff MS. 2013. Onset of breast development in a longitudinal cohort. *Pediatrics* 132(6):1019-1027. [[Synopsis](#)]

[Return to Table of Contents](#) | [Return to Papers of the Year](#)

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.

Researchers implanted mice with epithelial stem-like cells cultured from prostates of young, disease-free men. The mice were fed 100 or 250 micrograms of BPA per kilogram body weight for two weeks during the period in which the cells produced humanized prostate tissue. The BPA that the mice ingested 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.

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* 155\(3\):805-817. \[Synopsis\]](#)

[Return to Table of Contents](#) | [Return to Papers of the Year](#)

In-house research

tssRNAs associated with paused Pol II serve as scaffold for transcription factors

Researchers from NIEHS have found that nascent transcription start site-associated (tss) RNAs, produced and stably bound by RNA polymerase II (Pol II) that has paused during early elongation, could provide a target for the recruitment of factors that modulate gene expression. Since transcription is a critical step in the creation of proteins from information within the genome, this work may provide insight into environmentally responsive gene expression and identify novel approaches for treating disease.

The scientists developed a highly sensitive method of characterizing the dynamics of promoter-associated Pol II and tssRNAs generated during early elongation in fruit fly, or *Drosophila*, cells. They found that paused Pol II and associated tssRNAs were very stable, long-lived species, remaining near gene promoters for tens of minutes before resuming transcription elongation.

Citation: [Henriques T, Gilchrist DA, Nechaev S, Bern M, Muse GW, Burkholder A, Fargo DC, Adelman K. 2013. Stable pausing by RNA polymerase II provides an opportunity to target and integrate regulatory signals. *Mol Cell* 52\(4\):517-528. \[Synopsis\]](#)

[Return to Table of Contents](#) | [Return to Papers of the Year](#)

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. However, mutations in aprataxin 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.

The authors 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 distorts the RNA-DNA damage recognition pocket in the protein and blocks its ability to efficiently recognize and process RNA-DNA lesions. Understanding these molecular mechanisms may aid in new therapies for neurological diseases and certain types of cancer.

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. [[Synopsis](#)] [[Story](#)]

[Return to Table of Contents](#) | [Return to Papers of the Year](#)

Human obesity increases colon cancer risk

A research team led by NIEHS scientists determined that obesity, rather than diet, causes changes in the colon that may lead to colorectal cancer.

The researchers fed two groups of mice a high-fat diet. The first contained a human version of the gene NAG-1, which protects against colon cancer, and the second lacked the gene. The NAG-1 group did not gain weight, while the second group grew plump and exhibited histone acetylation patterns in isolated colon cells that resembled patterns from mice with colorectal cancer. The additional weight carried by this group also activated genes that helped promote the rapid progression of cancer.

The findings suggest that preexisting colon lesions in obese individuals are more likely to rapidly evolve into malignant tumors. The results also provide further evidence that calorie control and frequent exercise may be keys to lowering risk.

Citation: [Li R, Grimm SA, Chrysovergis K, Kosak K, Wang X, Du Y, Burkholder A, Janardhan K, Mav D, Shah R, Eling TE, Wade PA](#). 2014. Obesity, rather than diet, drives epigenomic alterations in colonic epithelium resembling cancer progression. *Cell Metab* 19(4):702-711. [[Synopsis](#)] [[Story](#)]

[Return to Table of Contents](#) | [Return to Papers of the Year](#)

INO80 regulates embryonic stem cell fate and blastocyst development

NIEHS researchers and their collaborators discovered that the INO80 complex maintains the pluripotency of embryonic stem cells (ESCs), allowing them to remain undifferentiated. Their findings provide insights into how ESCs selectively activate pluripotency genes and repress differentiation genes.

Using a combination of molecular biology, biochemistry, and systems biology techniques, the scientists showed that INO80 occupies promoters of genes involved in ESC self-renewal and pluripotency. INO80 does so with help from transcription factor OCT4 and histone methyltransferase complex component WDR5 — two other key pluripotency proteins.

The researchers also observed an increase in INO80 expression during early embryonic development, reaching its peak at the blastocyst stage. INO80 expression in the blastocyst is required to establish pluripotency in the inner cell mass, which ultimately forms the embryo.

Citation: Wang L, Du Y, Ward JM, Shimbo T, Lackford B, Zheng X, Miao YL, Zhou B, Han L, Fargo DC, Jothi R, Williams CJ, Wade PA, Hu G. 2014. INO80 facilitates pluripotency gene activation in embryonic stem cell self-renewal, reprogramming, and blastocyst development. *Cell Stem Cell* 14(5):575-591. [[Synopsis](#)]

[Return to Table of Contents](#) | [Return to Papers of the Year](#)

GWAS meta-analysis reveals new DNA loci of lung function

NIEHS researchers and their collaborators in a global consortium identified six new loci — specific regions of the genetic code — associated with individual variations in a widely used clinical measure of lung function. The genetic variants appear to influence an individual's forced vital capacity (FVC), a measure used to diagnose and monitor lung diseases. The new loci may shed light on mechanisms involved in lung development and the pathogenesis of lung diseases.

Using a large-scale meta-analysis approach, the scientists analyzed the results of genome-wide association studies (GWAS) in 52,253 individuals from 26 countries. They followed up the FVC associations in 32,917 additional individuals of European descent. The study identified six new regions associated with FVC that had not been seen in previous GWAS lung function studies.

The newly implicated regions were also studied in samples from African-American, Korean, Chinese, and Hispanic individuals.

Citation: Loth DW, Artigas MS, Gharib SA, Wain LV, Franceschini N, Koch B, Pottinger TD, Smith AV, Duan Q, Oldmeadow C, Lee MK, Strachan DP, James AL, Huffman JE, Vitart V, Ramasamy A, Wareham NJ, Kaprio J, Wang XQ, Trochet H, Kahonen M, Flexeder C, Albrecht E, Lopez LM, de Jong K, Thyagarajan B, Alves AC, Enroth S, Omenaas E, Joshi PK, Fall T, Vinuela A, Launer LJ, Loehr LR, Fornage M, Li G, Wilk JB, Tang W, Manichaikul A, Lahousse L, Harris TB, North KE, Rudnicka AR, Hui J, Gu X, Lumley T, Wright AF, Hastie ND, Campbell S, Kumar R, Pin I, Scott RA, Pietilainen KH, Surakka I, Liu Y, Holliday EG, Schulz H, Heinrich J, Davies G, Vonk JM, Wojczynski M, Pouta A, Johansson A, Wild SH, Ingelsson E, Rivadeneira F, Volzke H, Hysi PG, Eiriksdottir G, Morrison AC, Rotter JI, Gao W, Postma DS, White WB, Rich SS, Hofman A, Aspelund T, Couper D, Smith LJ, Psaty BM, Lohman K, Burchard EG, Uitterlinden AG, Garcia M, Joubert BR, McArdle WL, Musk AB, Hansel N, Heckbert SR, Zgaga L, van Meurs JB, Navarro P, Rudan I, Oh YM, Redline S, Jarvis DL, Zhao JH, Rantanen T, O'Connor GT, Ripatti S, Scott RJ, Karrasch S, Grallert H, Gaddis NC, Starr JM, Wijmenga C, Minster RL, Lederer DJ, Pekkanen J, Gyllensten U, Campbell H, Morris AP, Glaser S, Hammond CJ, Burkart KM, Beilby J, Kritchevsky SB, Gudnason V, Hancock DB, Williams OD, Polasek O, Zemunik T, Kolcic I, Petrini MF, Wjst M, Kim WJ, Porteous DJ, Scotland G, Smith BH, Viljanen A, Heliovaara M, Attia JR, Sayers I, Hampel R, Gieger C, Deary IJ, Boezen HM, Newman A, Jarvelin MR, Wilson JF, Lind L, Stricker BH, Teumer A, Spector TD, Melen E, Peters MJ, Lange LA, Barr RG, Bracke KR, Verhamme FM, Sung J, Hiemstra PS, Cassano PA, Sood A, Hayward C, Dupuis J, Hall IP, Brusselle GG, Tobin MD, London SJ. 2014. Genome-wide association analysis identifies six new loci associated with forced vital capacity. *Nat Genet* 46(7):669-677. [[Synopsis](#)] [[Story](#)]

[Return to Table of Contents](#) | [Return to Papers of the Year](#)

Humans with APOE4 gene more prone to inflammation

NIEHS scientists and their colleagues are the first to report that people with a particular form of the lipid-regulating gene apolipoprotein E (APOE) — specifically the APOE4 allele — may be more prone to inflammation than others.

The researchers used the NIEHS [Environmental Polymorphisms Registry](#) to identify healthy volunteers, based on their APOE genotype. Using the NIEHS Clinical Research Unit to obtain and examine the samples, they found that whole blood from patients with at least one copy of APOE4 produced a more robust inflammatory response to lipopolysaccharide, a surface component of bacteria, than blood from patients who didn't express APOE4.

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

Citation: Gale SC, Gao L, Mikacenic C, Coyle SM, Rafaels N, Murray Dudenkov T, Madenspacher JH, Draper DW, Ge W, Aloor JJ, Azzam KM, Lai L, Blackshear PJ, Calvano SE, Barnes KC, Lowry SF, Corbett S, Wurfel MM, Fessler MB. 2014. APOepsilon4 is associated with enhanced in vivo innate immune responses in human subjects. *J Allergy Clin Immunol* 134(1):127-134. [[Synopsis](#)] [[Story](#)]

[Return to Table of Contents](#) | [Return to Papers of the Year](#)

Control of histone expression by phosphorylation of an mRNA processing protein

By examining phosphorylation of the stem-loop-binding protein (SLBP), which has a role in processing histone mRNA, NIEHS scientists and their collaborators detailed a new method of histone expression regulation. This research is important because levels of histones, proteins that package DNA within the nucleus, have to be controlled throughout the cell cycle. During DNA replication, histone levels must increase to package new DNA, but following replication, extra histones are toxic to the cell.

Using biochemical assays, the scientists found that phosphorylation of SLBP at two different regions increases the ability of the protein to bind RNA. Interestingly, phosphorylation at the protein C-terminus increases RNA binding without actually coming into contact with the RNA. Further crystallography and nuclear magnetic resonance experiments showed that phosphorylation of this region caused a conformational change that increases RNA-binding abilities of the whole protein.

Citation: Zhang J, Tan D, DeRose EF, Perera L, Dominski Z, Marzluff WF, Tong L, Hall TM. 2014. Molecular mechanisms for the regulation of histone mRNA stem-loop-binding protein by phosphorylation. *Proc Natl Acad Sci U S A* 111(29):E2937-E2946. [[Synopsis](#)]

[Return to Table of Contents](#) | [Return to Papers of the Year](#)

Histone-fold domain protein NF-Y promotes chromatin accessibility for cell specification

NIEHS researchers have unearthed a novel function for NF-Y in promoting chromatin accessibility and specification of cell identity. Histone-fold protein NF-Y, a ubiquitously expressed transcription factor, was previously known for its role in the regulation of cell cycle progression in proliferating cells.

The authors investigated NF-Y's function and mechanism of action using genome-wide occupancy and transcriptomic analyses in embryonic stem cells and neurons. They discovered that NF-Y uses distinct modes to regulate housekeeping and cell identity programs. While NF-Y regulates housekeeping genes through cell type-invariant promoter-proximal binding, the findings demonstrated that NF-Y regulates genes required for cell identity by binding to cell type-specific enhancers. At enhancers, NF-Y promotes the binding of master transcription factors by facilitating a permissive chromatin conformation. Based on these results, the authors propose a potential mechanism for NF-Y in recruiting pioneer transcription factors for cell specification.

Citation: Oldfield AJ, Yang P, Conway AE, Cinghu S, Freudenberg JM, Yellaboina S, Jothi R. 2014. Histone-fold domain protein NF-Y promotes chromatin accessibility for cell type-specific master transcription factors. *Mol Cell* 55(5):708-722. [[Synopsis](#)]

[Return to Table of Contents](#) | [Return to Papers of the Year](#)

SIRT1 regulates retinoic acid signaling and stem cell differentiation

NIEHS researchers and their collaborators demonstrated that stem cell differentiation signals stemming from retinoic acid (RA), an active metabolite of vitamin A, involve the cellular metabolic sensor sirtuin 1 (SIRT1). SIRT1 is a protein deacetylase that coordinates the activation of transcription factors in response to cellular stress, which allows the cell to react to environmental cues.

In mice, deletion of SIRT1 results in embryonic lethality and severe developmental defects in surviving offspring. The authors show that loss of SIRT1 in mouse embryonic stem cells accelerates RA-induced differentiation. They also determined that hyperacetylation of cellular retinoic acid binding protein II (CRABP II) at amino acid K102 is partially responsible for the RA-mediated hyperdifferentiation of SIRT1-deficient embryonic stem cells. Understanding the signaling pathways that SIRT1 mediates will provide insight into how the environment affects mammalian development.

Citation: Tang S, Huang G, Fan W, Chen Y, Ward JM, Xu X, Xu Q, Kang A, McBurney MW, Fargo DC, Hu G, Baumgart-Vogt E, Zhao Y, Li X. 2014. SIRT1-mediated deacetylation of CRABP II regulates cellular retinoic acid signaling and modulates embryonic stem cell differentiation. *Mol Cell* 55(6):843-855. [[Synopsis](#)]

[Return to Table of Contents](#) | [Return to Papers of the Year](#)

Maternal smoking linked to altered DNA in newborns

New research demonstrates that mothers who choose to smoke during pregnancy may actually alter their offspring's epigenetic DNA profile. In one of the largest studies of its kind to date, researchers from NIEHS and Norway have identified specific modified regions in the genomes of children from mothers who smoked during pregnancy.

Examining DNA methylation marks in blood collected from 889 newborns, with 287 newborns from mothers with self-reported smoking during the first trimester, the scientists discovered altered methylation patterns in or near 110 genes. Some of these genes are related to the ability to quit smoking, nicotine addiction, and fetal development.

This work adds to a body of evidence that maternal exposure and behavior can modify DNA during fetal development. More research is needed to understand the persistence of these DNA alterations as children mature.

Citation: [Markunas CA](#), [Xu Z](#), [Harlid S](#), [Wade PA](#), [Lie RT](#), [Taylor JA](#), [Wilcox AJ](#). 2014. Identification of DNA methylation changes in newborns related to maternal smoking during pregnancy. *Environ Health Perspect* 122(10):1147-1153. [[Synopsis](#)]

[Return to Table of Contents](#) | [Return to Papers of the Year](#)

Duking it out? My CA2 made me do it

In collaboration with the National Institute of Mental Health, researchers at NIEHS have discovered that activation of the vasopressin 1b receptor (Avpr1b) in a certain part of the brain is necessary for social aggression. Within the brain, this receptor is expressed uniquely in the CA2 region of the hippocampus, a part of the brain more commonly associated with learning and memory.

To understand the mechanism of Avpr1b action, scientists measured the synaptic strength in brain slices from rats and mice. They found that vasopressin caused synaptic potentiation, but only in the CA2. Further studies indicated this response was exactly the same as that induced by oxytocin, which is another social neuropeptide. This research could lead to exciting new treatments for patients with psychiatric disorders who have inappropriate social aggression.

Citation: [Pagani JH](#), [Zhao M](#), [Cui Z](#), [Williams Avram SK](#), [Caruana DA](#), [Dudek SM](#), [Young WS](#). 2014. Role of the vasopressin 1b receptor in rodent aggressive behavior and synaptic plasticity in hippocampal area CA2. *Mol Psychiatry*; doi:10.1038/mp.2014.47 [Online 27 May 2014]. [[Synopsis](#)] [[Story](#)]

[Return to Table of Contents](#) | [Return to Papers of the Year](#)

DNA replication errors in yeast offer new insight into cancer research

NIEHS researchers have discovered new information regarding the DNA replication error rate of yeast, and the efficiency with which the mismatch repair system (MMR) can correct these errors. The findings could help scientists understand mutations in both evolutionary processes and human cancers and identify mutations that drive cancer formation.

By sequencing 70 nuclear genomes from eight yeast strains with a variety of MMR and polymerase defects, the researchers collected 40,000 mutations. From observed error rates, they concluded that MMR corrects more than 99 percent of all mismatches. They found that MMR efficiency and replication fidelity are influenced by mismatch type, the responsible polymerase, timing of replication, and replication origin proximity. Mutation rates also vary by replication fork direction, protein coding state, nucleosome proximity, and sequence context. Mutation patterns established in this work explain patterns in hypermutated endometrial cancers.

Citation: Lujan SA, Clausen AR, Clark AB, MacAlpine HK, MacAlpine DM, Malc EP, Mieczkowski PA, Burkholder AB, Fargo DC, Gordenin DA, Kunkel TA. 2014. Heterogeneous polymerase fidelity and mismatch repair bias genome variation and composition. *Genome Res* 24(11):1751-1764. [[Synopsis](#)]

[Return to Table of Contents](#) | [Return to Papers of the Year](#)

National Toxicology Program research

NTP finds a better animal model to evaluate the effects of chemical exposure

Researchers from NTP have used a genetically diverse mouse model to predict the range of toxicity that might be observed in humans after exposure to benzene, a common air pollutant and known human carcinogen. Using Diversity Outbred (DO) mice, the study estimates a benzene exposure threshold of 0.205 parts per million, which is consistent with observations of response in humans, but is well below the value previously obtained using inbred mice.

Since micronuclei are standard biomarkers of chromosomal damage, the scientists measured the frequency of micronucleated red blood cells in each genetically unique DO mouse before and after inhalation exposure to benzene. Using genetic mapping and linkage analysis, the authors identified a locus associated with resistance to benzene-induced genotoxicity on mouse chromosome 10. Sulfotransferases located in this region are likely candidate genes for benzene resistance.

Citation: French JE, Gatti DM, Morgan DL, Kissling GE, Shockley KR, Knudsen GA, Shepard KG, Price HC, King D, Witt KL, Pedersen LC, Munger SC, Svenson KL, Churchill GA. 2014. Diversity outbred mice identify population-based exposure thresholds and genetic factors that influence benzene-induced genotoxicity. *Environ Health Perspect*; doi:10.1289/ehp.1408202 [Online 6 November 2014]. [[Synopsis](#)]

[Return to Table of Contents](#) | [Return to Papers of the Year](#)

NTP research finds low doses of inorganic arsenic cause lung tumors in male mice

NTP researchers found that exposure to low doses of inorganic arsenic caused lung tumors in male mice. The researchers used a model that duplicated how humans are exposed to arsenic throughout their lifetime. Mice were given 50 parts per billion (ppb), 500 ppb, and 5,000 ppb of inorganic arsenic in their drinking water three weeks before breeding and throughout pregnancy and lactation. Arsenic was then given to offspring after weaning and throughout adulthood.

More than half of the male offspring developed significant increases in benign and malignant lung tumors at the two lower doses.

Citation: Waalkes MP, Qu W, Tokar EJ, Kissling GE, Dixon D. 2014. Lung tumors in mice induced by “whole-life” inorganic arsenic exposure at human-relevant doses. *Arch Toxicol* 88(8):1619-1629. [[Synopsis](#)] [[Story](#)]

[Return to Table of Contents](#) | [Return to Papers of the Year](#)

NTP review framework addresses environmental health questions

Scientists in the NTP Office of Health Assessment and Translation (OHAT) published a flexible seven-step process to streamline the development of hazard identification conclusions. The principles of this systematic review process are intended to help environmental health scientists integrate evidence from a variety of sources.

In 2011, OHAT began consulting technical experts, the NTP Board of Scientific Counselors, the public, and others to develop an efficient and standardized systematic review approach for literature-based environmental health science assessments. The resulting seven-step framework provides guidance on problem formulation and protocol development, searching and selecting studies for inclusion, extracting data from studies, assessing the quality of individual studies, rating confidence in the body of evidence, translating confidence ratings into evidence of health effects, and integrating evidence to develop hazard identification conclusions.

Citation: Rooney AA, Boyles AL, Wolfe MS, Bucher JR, Thayer KA. 2014. Systemic review and evidence integration for literature-based environmental health science assessments. Environ Health Perspect 122(7): 711–718. [Synopsis]

[Return to Table of Contents](#) | [Return to Papers of the Year](#)

The impacts of air pollution on the immune system

By Robin Arnette

As a pediatric immunologist and NIEHS grantee, Kari Nadeau, M.D., Ph.D., knows that environmental exposures may have serious effects on human health. That’s why she teamed up with researchers from several universities in California, as well as NIEHS and the U.S. Environmental Protection Agency, to form the [Children’s Health and Air Pollution Study – San Joaquin Valley](#). The study aims to understand and reduce the risks of air pollution exposure to children living in California’s San Joaquin Valley.

[Nadeau](#) is associate professor of Pediatrics – Allergy and Immunology at Stanford University School of Medicine. She talked about the study, collaborations, and scientific insights that have resulted, during a Dec. 16 NIEHS Distinguished Lecture, “How Pollution Exposure Leads to Immune Dysfunction: The Role of Epigenetics and Multiplex Immunophenotyping Studies.” Gwen Collman, Ph.D., NIEHS Division of Extramural Research and Training director, served as seminar host.

Environmental exposures and disease outcomes

One of the things that prompted Nadeau to examine the effects of pollution on children was a World Health Organization report she read as a young pediatrician. According to the report, more than 33 percent of diseases in children age 5 and younger result from environmental exposures. With most risk factors related to air and water pollution, pesticides, and contaminants in the diet, Nadeau knew the immune system was playing a critical role.



“With the Children’s Environmental Health Centers, we’re working to educate the community about what the science is telling us, and how it may help the community and help shape public health policy,” Nadeau said. (Photo courtesy of Steve McCaw)

“Both the innate and adaptive immune systems are sensitive to these detrimental environmental exposures and can tell us a lot about how our body reacts to toxicants,” Nadeau said.

Nadeau studies regulatory T cells — cells that modulate the immune system — to form hypotheses about the link between the immune system and asthma. Though her group focuses on asthma, pollution may worsen defects in a person’s immune system, resulting in diseases such as endocrine disorders, allergic reactions, cancer, cardiovascular disease, and autoimmune disease.

NIEHS advice spurs new research connection

Nadeau, who specializes in molecular immunology, had been looking for ways to test her hypotheses. She decided to call NIEHS and was advised to collaborate with Ira Tager, M.D., professor of epidemiology at the University of California, Berkeley. For several years, Tager had been studying children with asthma and allergies in Fresno and the surrounding San Joaquin Valley, one of the most polluted areas of the country, with fine particulate matter in air exceeding the federal annual standard by more than 40 percent.

Tager and Nadeau worked together to develop four cohorts of healthy and asthmatic children at both Stanford and Berkeley. They collected blood from 367 children and measured surrounding particulate matter, air pollutants, polycyclic aromatic hydrocarbons, volatile organic compounds, smoke, and allergens.

The study found a 3-fold increase in a special set of cells, called ILC2-like cells, in children with high exposure to air pollution. The findings are the first to show that ILC2-like cells are associated with high pollution exposure in humans.

Donald Cook, Ph.D., head of the NIEHS Immunogenetics Group noted innovative aspects of the work. “Their research used a new technology called time-of-flight mass cytometry, which allowed a large number of different antibodies to be used simultaneously,” he said “This work definitely pushes the field of immunology further along.”



“Since Kari has been a grantee of the institute for some time, I’m familiar with the proposals she has submitted,” Collman said. “I thought it would be great to hear her talk about the work we currently fund.” (Photo courtesy of Steve McCaw)



Cook’s research group uses genetic approaches to understand the molecular and cellular mechanisms that lead to responses to inhaled allergens. (Photo courtesy of Steve McCaw)

Linked video: (Launches in new window)
Watch Nadeau discuss her insights into biomarkers for the success of clinical immune therapy, in an interview with the editor of the *Journal of Allergy and Clinical Immunology*, which published a 2014 paper on these findings. (8:33)

Download Media Player: Flash

Heavy metals in water

Nadeau also discussed her role in the New Hampshire Birth Cohort Study, which examines the impact of environmental factors on pregnancy and child health. Many residents of New Hampshire use privately owned wells, which often contain high levels of arsenic. Nadeau worked with Margaret Karagas, Ph.D., of Dartmouth College to evaluate arsenic and cadmium exposure in area pregnant mothers and their children.

Looking back on her involvement in these studies, Nadeau said her training was an asset. “I wanted to approach the problem as a clinician scientist, as a translational researcher, and as an immunologist,” she said. “It’s great that we can be cross-trained in immunology, as well as other fields.”

[Return to Table of Contents](#)



Michael Fessler, M.D., deputy chief of the NIEHS Immunity, Inflammation, and Disease Laboratory, and head of the Clinical Investigation of Host Defense Group, was particularly interested in Nadeau’s findings related to the innate immune response. (Photo courtesy of Steve McCaw)

NIEHS scientists determine how environment contributes to several human diseases

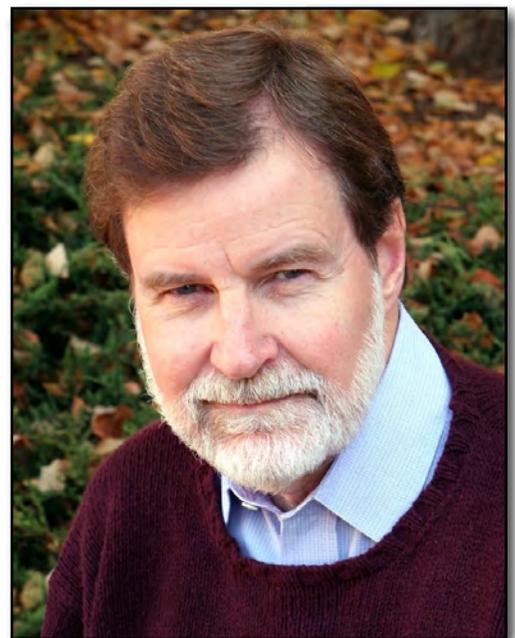
By Robin Arnette

Using a new imaging technique, NIEHS researchers have found that the biological machinery that builds DNA can insert into the DNA strand molecules that have been damaged by environmental exposures. These damaged molecules trigger cell death that produces some human diseases, according to the researchers.

The [work](#), appearing online Nov. 17 in the journal *Nature*, provides a possible explanation for how one type of DNA damage may lead to cancer, diabetes, hypertension, cardiovascular and lung disease, and Alzheimer’s disease.

Time-lapse crystallography was used by the researchers to determine that DNA polymerase, the enzyme responsible for assembling the nucleotides or building blocks of DNA, incorporates nucleotides with a specific kind of damage into the DNA strand. Time-lapse crystallography is a technique that takes snapshots of biochemical reactions occurring in cells.

Samuel Wilson, M.D., senior NIEHS researcher on the team, explained that the damage is caused by oxidative stress, or the generation of free oxygen molecules, in response to environmental factors, such as ultraviolet exposure, diet, and chemical compounds in paints, plastics, and other consumer products. He said scientists suspected that the DNA polymerase was inserting nucleotides that were damaged by carrying an additional oxygen atom.



Wilson was honored in April with the 2014 Southeast Regional Collaborative Access (SER-CAT) Team Outstanding Science Award for his expertise with the use of macromolecular crystallography in his structural biology studies. (Photo courtesy of Steve McCaw)

“When one of these oxidized nucleotides is placed into the DNA strand, it can’t pair with the opposing nucleotide as usual, which leaves a gap in the DNA,” Wilson said. “Until this paper, no one had actually seen how the polymerase did it or understood the downstream implications.”

Wilson and his colleagues saw the process in real time, by forming crystal complexes made of DNA, polymerase, and oxidized nucleotides, and capturing snapshots at different time points through time-lapse crystallography. The procedure not only uncovered the stages of nucleotide insertion, but also indicated that the new DNA stopped the DNA repair machinery from sealing the gap. This fissure in the DNA prevented further DNA repair and replication, or caused an immediate double-strand break.

“The damaged nucleotide site is akin to a missing plank in a train track,” Wilson said. “When the engine hits it, the train jumps the track, and all of the box cars collide.”

Large numbers of these pileups and double-strand breaks are lethal to the cell, serving as a jumping off point for the development of disease. However, it can be a good thing if you are a researcher trying to destroy a cancer cell.

“One of the characteristics of cancer cells is that they tend to have more oxidative stress than normal cells,” said Bret Freudenthal, Ph.D., lead author of the paper and postdoctoral fellow in Wilson’s group. “Cancer cells address the issue by using an enzyme that removes oxidized nucleotides that otherwise would be inserted into the genome by DNA polymerases. Research performed by other groups determined if you inhibit this enzyme, you can preferentially kill cancer cells.”

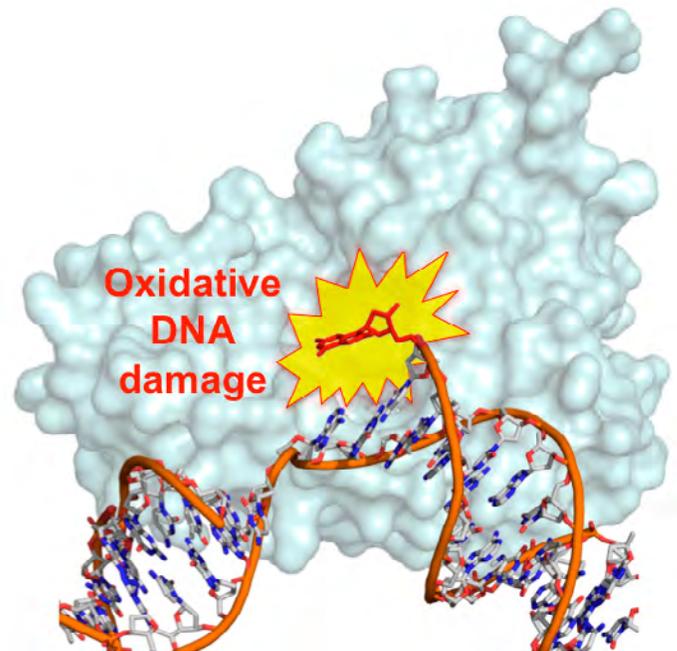
Wilson and Freudenthal stressed that the quantities of oxidized nucleotides in the nucleotide pool are usually under tight control, but if they accumulate and start to outnumber undamaged nucleotides, the DNA polymerase adds more of them to the strand. Molecules that inhibit oxidation, known as antioxidants, reduce the level of oxidized nucleotides, and may help prevent some diseases.

Citation: [Freudenthal BD, Beard WA, Perera L, Shock DD, Kim T, Schlick T, Wilson SH. 2014. Uncovering the polymerase-induced cytotoxicity of an oxidized nucleotide. Nature; doi:10.1038/nature13886 \[Online 17 November 2014\]. \[Summary\]\(#\)](#)

[Return to Table of Contents](#)



Freudenthal was a presenter at the annual Mid-Atlantic Macromolecular Crystallography Meeting this spring at Duke University. (Photo courtesy of Steve McCaw)



After the DNA polymerase (gray molecule in background) inserts a damaged nucleotide into DNA, the damaged nucleotide is unable to bond with its undamaged partner. As a result, the damaged nucleotide swings freely within the DNA, interfering with the repair function or causing double-strand breaks. These steps may ultimately lead to several human diseases. (Graphic courtesy of Bret Freudenthal)

Woodruff explores the next generation of tissue chip development

By Eddy Ball

According to Teresa Woodruff, Ph.D., *in vitro* predictive toxicology is poised to take the next big step in modeling, from single-dimension to multi-dimension integrated tissue cultures.

“This is a story that’s really emerging,” Woodruff told her audience, during a Dec. 4 guest lecture at NIEHS. David Balshaw, Ph.D., program administrator and head of the NIEHS Exposure, Response, and Technology Branch, enthusiastically agreed. “This is one of the most exciting projects in my portfolio,” he said.

Woodruff is a distinguished professor of obstetrics and gynecology, director of the Women’s Health Research Institute at Northwestern University, and immediate past president of the Endocrine Society. She is also the lead researcher on an innovative [grant](#) to develop an *ex vivo* microfluidic reproductive tract model.

This grant is funded by NIEHS, the National Center for Advancing Translational Sciences, the Office of Women’s Health Research, and the Eunice Kennedy Shriver National Institute of Child Health and Human Development — all part of the National Institutes of Health.

Modeling the female reproductive tract and hormonal cycle *in vitro*

As Woodruff explained, her modeling projects are striving to address the issue of extrapolation from cell cultures and other species to humans. Her FemKUBE is a distinct 3-D tissue-engineered model of the female reproductive tract, including the ovarian follicle, fallopian tube, uterus, and cervix. Woodruff’s goal is to physically link them, but currently they are stand-alone models.

While preclinical toxicity testing in animal models is a cornerstone of the drug development process, it can be controversial and expensive, and it is often unable to predict adverse effects and tolerability issues in human subjects. Predictive toxicology is increasingly exploring alternatives, such as *in vitro* high-throughput screening and tissue chip models, to prioritize chemicals and address the massive backlog of untested compounds.



Woodruff is a dynamic speaker who uses movement, gesture, and eye contact to capture the audience’s attention and communicate enthusiasm for her work. (Photo courtesy of Steve McCaw)



Woodruff credited Balshaw, left, with helping sell her proposal to reviewers. Along with his colleagues from the NIEHS Division of Extramural Research and Training, several in-house lead researchers attended the talk, including Carmen Williams, M.D., Ph.D., right, head of the Reproductive Medicine Group. (Photo courtesy of Steve McCaw)

Even though Woodruff is the first to admit there are many challenges ahead, her team has already defied conventional wisdom with the ability of its FemKUBE model to mimic, with unprecedented fidelity, the elegant hormonal orchestration of the dynamic 28-day female menstrual cycle. FemKUBE uses mouse follicle, but the rest of the model — the cervix, vagina, uterus, fallopian tube, and ovary — consists entirely of human tissue.

Woodruff has used FemKUBE to assess the impact of exposures on the female reproductive tract, including known endocrine disruptors and reproductive toxicants, as well as compounds with unknown toxicity, such as the oil dispersant Corexit, which was used following the 2010 Deepwater Horizon oil spill.

Working toward a human on a chip

While Woodruff's work, to date, has focused on female reproduction, she is looking beyond women with the concept of a comprehensive repro-on-a-chip model. She considers the development of female and male (DudeKUBE) reproductive microfluidic systems as critical to sex-based *in vitro* toxicity and drug testing.

One motivation for starting with the FemKUBE, Woodruff explained, was the critical and underappreciated role of hormone signaling in health and disease throughout the body. With [tissue chip grants](#) awarded in 2012 and 2014, other tissue culture developers are working on models, such as heart-liver-vascular systems, circulatory system and integrated muscle tissue, neurovascular system, kidney, stem cells, and specific diseases and disease processes.

These models represent an important step toward integration of individual organs and systems into a so-called human-on-a-chip model for mimicking health effects throughout the human body.

Citation: [Eddie SL](#), [Kim JJ](#), [Woodruff TK](#), [Burdette JE](#). 2014. Microphysiological modeling of the reproductive tract: a fertile endeavor. *Exp Biol Med* (Maywood) 239(9):1192-1202.

[Return to Table of Contents](#)



National Toxicology Program scientists were also on hand for the presentation, including postdoctoral fellows [Natasha Catlin, Ph.D.](#), left, of the Developmental and Reproductive Toxicology Group, and [Georgia Hinkley, Ph.D.](#), of the General Toxicology and Cancer Group. (Photo courtesy of Steve McCaw)

The potential of tissue chip models

Now in development in Woodruff's lab, 3-D microdynamic models of the reproductive system promise to pave the way for important discoveries, such as the following:

- Better understanding sex-based differences in response to drugs and environmental exposures
- Improving fertility treatment, including oncofertility for reproductive issues related to cancer treatment
- Determining response to hormones and endocrine-disrupting chemicals, particularly for vulnerable populations
- Providing a human correlate for drug development, especially for those medications given to pregnant women
- Advancing predictive toxicology and disease prevention

Triclosan promotes liver tumor growth in mice, say SRP researchers

By Sara Mishamandani

A collaborative study performed by NIEHS-funded scientists from the University of California (UC) San Diego and UC Davis showed that long-term exposure to triclosan promotes the growth of liver tumors in laboratory mice, raising concerns about its safety for humans. Triclosan is a common antibacterial chemical used in a wide variety of consumer products such as cosmetics, soaps, detergents, and toothpaste.

“Triclosan’s increasing detection in environmental samples and its increasingly broad use in consumer products may overcome its moderate benefit and present a very real risk of liver toxicity for people,” said study leader Robert Tukey, Ph.D., director of the Superfund Research Program (SRP) Center at UC San Diego. Tukey led the study with Bruce Hammock, Ph.D., director of the UC Davis SRP Center.

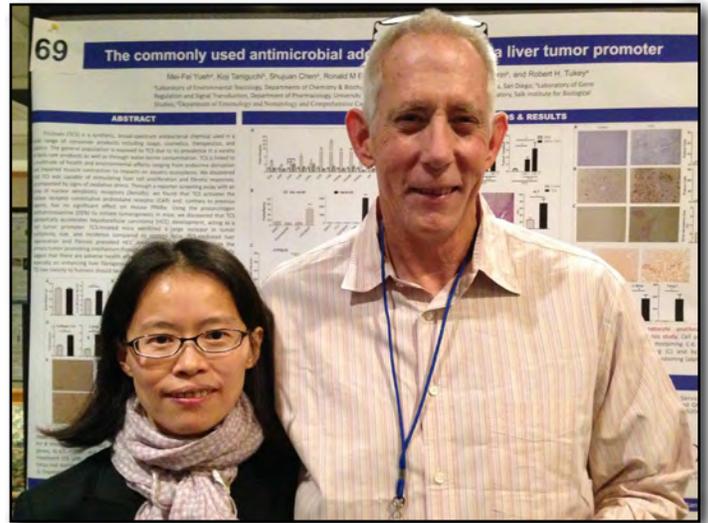
Investigating health effects of triclosan

The authors investigated long-term exposure to triclosan in mice by treating them with triclosan for 6 months, which is roughly equivalent to 18 human years. They then compared the livers of exposed mice with those of mice not exposed to triclosan. Researchers found that chronic exposure to triclosan in mice caused liver damage and liver cell death. They also discovered that triclosan exposure in mice increased susceptibility to tumor formation through enhanced cell growth, liver fibrosis (excessive accumulation of proteins in the liver), and proinflammatory responses, which are circumstances within which human cancer forms.

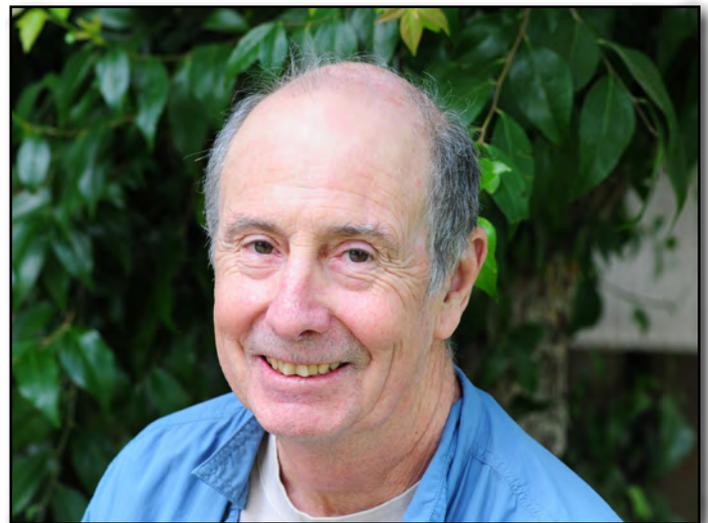
The scientists found that triclosan interferes with a nuclear receptor, known as the constitutive androstane receptor, that plays a role in detoxifying the blood. To compensate for this interference, the liver overproduces cells, which can lead to fibrosis and cancer.

Addressing a human health concern

Although the animal studies used higher concentrations than generally predicted for human exposure, the study indicates that triclosan can promote tumors in the liver and that the way triclosan acts on the mouse may be relevant to human physiology. The study authors concluded that because of this new evidence, the potential of triclosan to cause liver cancer in humans should be evaluated.



Tukey, right, is a joint professor in the Department of Pharmacology and the Department of Chemistry and Biochemistry. Mei-Fei Yueh, Ph.D., project scientist at UC San Diego, is the lead author on the paper. (Photo courtesy of Robert Tukey)



Hammock holds a joint appointment with the UC Davis Department of Entomology and Nematology, and the Comprehensive Cancer Center. (Photo courtesy of Kathy Garvey)

“We could reduce most human and environmental exposures by eliminating uses of triclosan that are high volume, but of low benefit, such as inclusion in liquid hand soaps,” said Hammock. “Yet we could also, for now, retain uses shown to have health value — as in toothpaste, where the amount used is small.”

Citation: [Yueh M-F, Taniguchi K, Chen S, Evans RM, Hammock BD, Karin M, and Tukey RH. 2014. The commonly used antimicrobial additive triclosan is a liver tumor promoter. Proc Natl Acad Sci U S A 111\(48\): 17200-17205. \[Summary\]\(#\)](#)

Hammock elected to National Academy of Inventors

Hammock was elected to the National Academy of Inventors Dec. 16, in recognition of his innovations in multiple fields of research and practical applications, such as therapeutic drugs and biosensor development.

According to the academy, election is accorded to academic inventors who have demonstrated a highly prolific spirit of innovation in creating or facilitating outstanding inventions that have made a tangible impact on quality of life, economic development, and the welfare of society.

For Hammock, this is yet another addition to his long list of awards (see related [story](#)). Hammock and his fellow nominees will be inducted March 20, 2015, during the academy’s fourth annual conference, at the California Institute of Technology in Pasadena.

(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.)

[Return to Table of Contents](#)

NTP advisors like what they hear at meeting

By Robin Mackar

Updates from National Toxicology Program (NTP) staff, which ranged from tests on chemicals spilled in West Virginia to systematic review and endocrine disruptor screening, were well received by the NTP Board of Scientific Counselors at their [meeting](#) Dec. 9-10 in Rodbell Auditorium.

West Virginia chemical spill research

Just five months after receiving a nomination from the Centers for Disease Control and Prevention Agency for Toxic Substances and Disease Registry, and meeting with West Virginia state and local officials about conducting additional [studies](#) on the chemicals spilled into the Elk River in West Virginia in 2014, NTP had a research plan in place and some early findings to share.

[Scott Auerbach, Ph.D.](#), of the NTP Biomolecular Screening Branch, presented a project overview, a timeline of activities, and introduced the board to eight different types of studies outlined in the plan. Auerbach provided a status update on each phase, from the least resource intensive — computational modeling, or structure-activity relationship analysis — to high-throughput testing, and then to the more complex rat prenatal toxicology studies. He also presented some early test results.

According to Auerbach, the 200 computational modeling scenarios completed by NTP helped determine the additional toxicology studies that are now being conducted. He also said that four of the spilled chemicals evaluated all tested negative using cell-based assays, which means they did not harm the cells they were tested against.

The research plan and study updates are available on the [NTP site](#), which will be updated as studies are completed. Board member Robert Chapin, Ph.D., of Pfizer, New York City, complimented NTP on its nimbleness and its plan to communicate findings rapidly and openly.

Assessing the biological relevance of *in vitro* data

Warren Casey, Ph.D., who leads the NTP Interagency [Center](#) for the Evaluation of Alternative Toxicological Methods gave a presentation describing how high-throughput screening methods provide results that are 97 percent similar to the animal-based screening method, which shows promise for the use of *in vitro* data to prioritize the testing of large numbers of chemicals.

Using a case study that NTP developed with the U.S. Environmental Protection Agency (EPA), Casey presented results from the testing of 86 chemicals in 16 integrated high-throughput screening methods that measure the ability of chemicals to interact with the human estrogen receptor. Results were compared to results from the animal-based test (rodent uterotrophic bioassay) required by EPA as part of their Endocrine Disruptor Screening Program for assessing estrogen receptor activity. The two assays provided the same results for most of the tested chemicals. “This is an amazing predictive tool for determining whether or not a chemical has the potential to interact with the human estrogen receptor,” Casey said.

Systematic review, Report on Carcinogens, effectiveness of NTP, and more

Other topics discussed with the board included an update on activities related to the Report on Carcinogens, including the August [peer review](#) of trichloroethylene; learning about the status of NTP nominations to be studied, including two flame retardants; and hearing results from a pilot project that assessed the reach and effectiveness of NTP studies. Using hexavalent chromium as an example, the NTP Office of Liaison, Policy, and Review used a [logic model](#) to document the impact that NTP research has had on many areas, including public health.



Board Chair Lisa Peterson, Ph.D., from the University of Minnesota, kept the meeting on schedule, despite a heavily packed agenda. Also shown are NTP Associate Director John Bucher, Ph.D., left, and NTP Associate Director Nigel Walker, Ph.D., right. (Photo courtesy of Steve McCaw)



Lori White, Ph.D., left, who serves as the Designated Federal Officer for the board, and Linda Birnbaum, Ph.D., NTP and NIEHS director, paid close attention to the discussions among the board members. (Photo courtesy of Steve McCaw)

The board also gave unanimous support for the Office of Health Assessment and Translation to move ahead with completing a systematic review of the literature looking at the effects on the immune system of two persistent chemicals, perfluorooctanic acid and perfluorooctane sulfonate. The Office started the evaluation as part of a case study to pilot test the seven-step systematic review and evidence integration approach developed by NTP to reach hazard identification conclusions.



Auerbach presented the variety of approaches being used by NTP to study the potential health hazards from chemicals spilled into the Elk River in West Virginia. (Photo courtesy of Steve McCaw)



Cherie Estill, Ph.D., from the National Institute for Occupational Safety and Health, provided updates on several collaborations between that institute and NIEHS, including looking into occupational exposures to bisphenol A, several flame retardants, and carbon nanotubes, and assessing manganese particles in welding fumes. (Photo courtesy of Steve McCaw)



Board members Mary Beth Genter, Ph.D., of the University of Cincinnati, and Chapin listen and advise on topics presented by NTP staff. (Photo courtesy of Steve McCaw)



One of the newer NTP staff members, Yun Xie, Ph.D., teamed with Mary Wolfe, Ph.D., deputy division director for policy, to present findings from a case study that showed how NTP findings on hexavalent chromium affected public health. (Photo courtesy of Steve McCaw)

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

[Return to Table of Contents](#)

Linking inflammation with environmental exposures

By Tara Ann Cartwright

A Dec. 11 webcast seminar highlighted the current research on inflammation by National Toxicology Program (NTP) scientists. This important disease process is the focus of a cross-divisional faculty at NIEHS, established pursuant to the 2012-2017 NIEHS Strategic Plan. Andrew Rooney, Ph.D., deputy director of the NTP Office of Health Assessment and Translation, and Nicole Kleinstreuer, Ph.D., a contractor who supports the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods, spoke on “Analysis and Predictive Toxicology Methods at NTP to Identify Biomarkers of Inflammation.”

Mamta Behl, Ph.D., a toxicologist in the NTP General Toxicology and Cancer Group, introduced both speakers. “The role of environmentally induced inflammation in health outcomes is an issue of longstanding interest to NIEHS and NTP and is very challenging in its scope,” she said.

Atherosclerosis — an answerable question

Chronic inflammation, which is also known as low-grade or systemic inflammation, is linked to numerous health effects and disease states. Despite the enormous interest of researchers, the details of this link remain unclear. According to Rooney, because of the large number of health effects and the vast literature on the subject, researchers are challenged to develop an answerable question related to linking exposure, the resulting inflammation, and ultimately, a health effect.

Rooney’s team set out to identify a single health effect with a manageable literature base, so they could evaluate the evidence using state-of-the-art analyses. Atherosclerosis, which has both a clear inflammatory mechanism associated with a range of environmental contaminants and a significant public health impact, satisfied their criteria.

Rooney’s strategy involved a two-pronged approach — the first was a systematic literature review process (see related [summary](#)) to evaluate evidence for the association between environmental exposures and biomarkers of inflammation, and the second was development of an adverse outcome pathway. The pathway approach describes molecular events between environmental exposure and a resulting adverse health outcome.

Rooney stressed that this project also evaluates the utility of the adverse outcome pathway as a tool. More importantly, the researchers hope to identify biomarkers of key events for use in future studies.



Rooney’s team is evaluating evidence that environmentally induced inflammation leads to serious health effects, including atherosclerosis. (Photo courtesy of Steve McCaw)



Kleinstreuer uses ToxCast Phase II data to help develop and test adverse outcome pathways for inflammation-driven health effects. (Photo courtesy of Steve McCaw)

High-throughput screening

Kleinstreuer reported on how high-throughput screening data, as used in the U.S. Environmental Protection Agency's [ToxCast](#) program, can be combined with literature review approaches to characterize the inflammatory pathway and identify biomarkers of environmental chemical exposure associated with inflammation-mediated adverse health outcomes.

To identify biomarkers, researchers stimulate human primary cells with various cytokine mixtures to mimic the tissue environment following chemical exposure. The scientists measure changes in expression of inflammatory and anti-inflammatory molecules.

According to Kleinstreuer, the aryl hydrocarbon receptor (AHR) showed promise. "A very small literature search shows that certain chemicals, such as polycyclic aromatic hydrocarbons, may trigger AHR to increase expression of certain cytokines, contributing to development inflammation and atherosclerotic plaque formation," she said, linking the predictive model with published research.

Primary human cell cultures used in predictive models may help establish a link between exposure to pollutants and the inflammatory pathway, Kleinstreuer noted in closing. "In tandem with the work [Rooney] is doing in systematic review of the literature, these tools and analyses are crucial to developing and testing an adverse outcome pathway for atherosclerosis," she said.

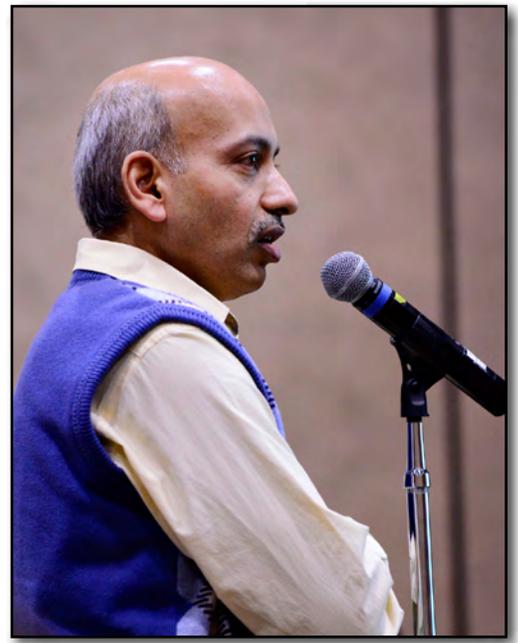
(Tara Ann Cartwright, Ph.D., is a former postdoctoral fellow in the NIEHS Intracellular Regulation Group).

[Return to Table of Contents](#)

Plant breeding models could aid toxicological research

By Ernie Hood

New computer modeling techniques, already in commercial use to enhance grain, fruit, and vegetable crops, may offer insights for animal modeling related to toxicology and toxicogenomics, according to Russell Wolfinger, Ph.D., the director of scientific discovery and genomics at SAS Institute, Inc., in Cary, North Carolina. Wolfinger spoke Dec. 16, in the latest offering from the NIEHS Data Science Seminar Series, hosted by the Office of Scientific Information Management (OSIM).



The format allowed ample time for attendees, both in person and via webcast, to raise questions on the work by Rooney and Kleinstreuer. Kyathanahalli Janardhan, Ph.D., is a pathologist in the NTP Immunohistochemistry Laboratory. (Photo courtesy of Steve McCaw)

Potential applications of predictive models to toxicological research

- Build genomic selection predictive models on mouse or rat lines
- Optimize animal line selection and potentially create new breeds for desired traits
- Optimize for microbes and viruses that interact with the environment, perhaps building in interaction with the microbiome

In a talk titled “Genomic Selection in Plant and Animal Breeding with Potential Applications to Toxicological Research,” Wolfinger showcased predictive models for quantitative biological traits. These models were developed for plant breeding and are now in heavy use by scientists at SAS’s commercial partner, General Mills, one of the largest food companies in the world. In a demanding marketplace, these models help breeders fine-tune desired traits in advance through sophisticated computational methods that have been validated and proven successful.

Computing firepower helps

Cross-validation of the models is critical. “There are literally millions of ways you can build these predictive models, so the question becomes, which models are going to do best, and which will work best in the future?” Wolfinger said. “We use the cross-validation approach to tackle those questions.”

“Once we have these predictive models in hand, they can be used effectively to accelerate progress around the breeding cycle,” he said. The plant breeders at General Mills use genotyping to improve and accelerate the breeding cycle, particularly in oats, which are the key ingredient of one of their flagship products, Cheerios.

In recent years, dramatic improvements in computing speed, memory, and cost have enhanced the ability of statisticians to crunch big data quickly. “Though some of these algorithms have been out in the literature for a while, they haven’t been very useful because they took too long to run,” Wolfinger observed. “Now, a breeder can sit at the computer and simulate literally years of potential work in just an afternoon,” he continued. “It’s really changing the game.”

Crossover possibilities

OSIM Director Allen Dearry, Ph.D., said the take-home message of Wolfinger’s talk was that the statistical methods he described could be applied to development of animal models used in toxicology. “In NTP [the National Toxicology Program], for example, researchers could carry out this same kind of quantitative modeling of genomic selection to better define or develop rodent models,” he said.

Wolfinger agreed. “For anything that you’re interested in measuring for potential use as a trait, if you think there’s a genomic component, a model could be built to predict it.” (See [sidebar](#) for examples.)

Wolfinger’s talk was co-sponsored by NTP and the NIEHS [predictive toxicology and disease](#) faculty.

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



Wolfinger, who has worked at SAS since 1989, leads a research team developing software solutions in the genomics and clinical research fields. (Photo courtesy of Steve McCaw)



“Wolfinger is a major star in the genomics and data science constellation,” said Dearry, above, in his introduction. (Photo courtesy of Steve McCaw)



Richard Paules, Ph.D., senior scientist for the Toxicogenomics and Genetics Group, and OSIM Data Scientist Rebecca Boyles were especially interested in Wolfinger's ideas. (Photo courtesy of Steve McCaw)



A full house of NIEHS and NTP researchers turned out for Wolfinger's Data Science Seminar Series lecture. (Photo courtesy of Steve McCaw)

[Return to Table of Contents](#)

Papers of note – cadmium, phthalates, and PAHs

By Kelly Lenox

Epidemiological study shows cadmium exposure is strongly associated with shortened leukocyte telomere length

In the largest study to date of exposure to metals and telomere length, researchers at the George Washington University Milken Institute School of Public Health, funded in part by NIEHS, have found a strong association between environmental exposures to cadmium and blood leukocyte telomere length.

Telomeres are DNA protein structures that protect the ends of chromosomes, and their shortening is associated with cell aging.

**Milken Institute School
of Public Health**

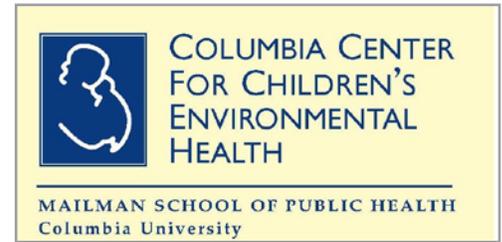
THE GEORGE WASHINGTON UNIVERSITY

Cadmium exposures may come from inhaling tobacco smoke, eating foods grown in soil high in cadmium, or occupational exposures. “While causality was not established, the study data is consistent with other findings of harmful effects of even low levels of cadmium on health,” said Kimberly McAllister, Ph.D., NIEHS health scientist administrator. Researchers also studied blood lead levels and found no relationship to telomere length.

Citation: Zota AR, Needham BL, Blackburn EH, Lin J, Park SK, Rehkopf DH, Epel ES. 2014. Associations of cadmium and lead exposure with leukocyte telomere length: findings from National Health and Nutrition Examination Survey, 1999-2002. Am J Epidemiol; doi:10.1093/aje/kwu293 [Online 10 Dec. 2014].

Researchers find link between exposure during pregnancy to certain phthalates and a drop in a child's IQ

NIEHS-funded researchers at the Columbia University Mailman School of Public Health are the first to report a link between prenatal exposure to two common phthalates and lowered IQ of 6 to 7 points in school-age children. "While much work remains to better understand the mechanisms, this study supports earlier work that points to mental and motor impacts of phthalate exposure on children," said Kimberly Gray, Ph.D., NIEHS health scientist administrator.



Citation: [Factor-Litvak P, Insel B, Calafat AM, Liu X, Perera F, Rauh VA, Whyatt RM.](#) 2014. Persistent associations between maternal prenatal exposure to phthalates on child IQ at age 7 years. *PLoS One* 9(12):e114003.

Scientists develop new technology to track polyaromatic hydrocarbons in humans

Researchers in the Oregon State University Superfund Research Program, supported in part by NIEHS, have developed a new application of accelerator mass spectrometry to track polyaromatic hydrocarbons (PAHs) as they move through the human body, providing new opportunities to study these potential cancer-causing compounds. "Knowing how people metabolize PAHs may verify a number of animal and cell studies, as well as provide a better understanding of how PAHs work," said Bill Suk, director of the NIEHS Superfund Research Program.



Citation: [Madeen E, Corley RA, Crowell S, Turteltaub K, Ognibene T, Malfatti M, McQuistan TJ, Garrard M, Sudakin D, Williams DE.](#) 2014. Human in vivo pharmacokinetics of [¹⁴C]Dibenzo[def,p]chrysene by accelerator mass spectrometry following oral microdosing. *Chem Res Toxicol*; doi:10.1021/tx5003996 [Online 10 Dec 2014].

[Return to Table of Contents](#)

This month in EHP

The January issue of *Environmental Health Perspectives (EHP)* looks at the challenges of maintaining hygiene to fight waterborne diseases during emergency situations, and extending regulation of dietary arsenic beyond drinking water by setting a limit for arsenic in rice.



<http://twitter.com/ehponline>

The WASH Approach: Fighting Waterborne Diseases in Emergency Situations

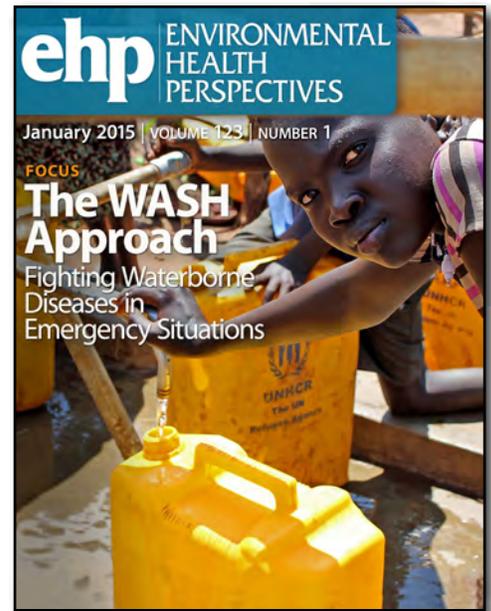
Emergency situations are ripe for outbreaks of diseases spread by fecal–oral transmission. In times of scarcity, water tends to go first to drinking and cooking, and hygiene become a lower priority. But health-protective behaviors are critically important for preventing the spread of waterborne diseases.

In Search of "Just Right:" The Challenge of Regulating Arsenic in Rice

Numerous studies have assessed the health impact of consuming arsenic through drinking water, and many countries regulate arsenic in municipal water. Now research and regulatory concerns are broadening to include arsenic in the diet, especially in rice, but settling on an appropriate limit for arsenic in rice is proving difficult.

Featured research and related news articles this month include:

- **ToxCast Wants You: Recommendations for Engaging the Broader Scientific Community** — A new commentary discusses two strategies for increasing engagement between ToxCast and researchers in disciplines beyond toxicology.
- **Inner Workings of Arsenic: DNA Methylation Targets Offer Clues to Mechanisms of Toxicity** — In a large study of Bangladeshi adults, researchers identify gene-specific DNA methylation targets in white blood cells.
- **“Exported” Deaths and Short-term PM10 Exposure: Factoring Into Mortality Estimates the Impact of Commuting** — A new report estimates mortality attributable to short-term PM10 exposure, using sophisticated models to account for two of the chief obstacles to assessing health impact — data uncertainty and mobility of the population.
- **Potential Mitochondrial Toxicants: Tox21 Screen Identifies Structures of Interest** — Scientists with the Tox21 consortium assessed the effect of more than 8,300 chemicals on mitochondrial membrane potential and cell viability.



[Return to Table of Contents](#)

Perera to discuss maternal exposures to the fetus in distinguished lecture

By Monica Frazier

The NIEHS Distinguished Lecture Series will feature a talk Jan. 13 by grantee Frederica Perera, Dr.P.H., Ph.D., of Columbia University. Her presentation, “The Fetal Window of Susceptibility: Using Molecular Epidemiology to Understand the Role of Prenatal Environmental Exposures on Child Health and Development,” will be hosted by NIEHS and National Toxicology Program Director Linda Birnbaum, Ph.D.

[Perera](#) is professor of environmental health sciences, and director of the NIEHS-funded [Columbia Center for Children’s Environmental Health](#), as well as the Disease Investigation Through Specialized Clinically-Oriented Ventures in Environmental Research ([DISCOVER](#)) Center. She is a leader in the field of molecular epidemiology, and focuses her research on exposures during early life, including the effects of prenatal exposures on development.

“Dr. Perera’s talk will no doubt attract a large audience at NIEHS,” Birnbaum said. “Her work is of considerable interest to many of our scientists, and directly relevant to the institute’s public health mission and the goals of our strategic plan.”



Perera is the author of more than 200 publications, including new research, funded by NIEHS, linking [ADHD](#) and air pollution. (Photo courtesy of Frederica Perera)

Perera investigates her hypotheses about environmental exposures through the use of prospective cohort studies, where people who share a common characteristic are studied over time. In Perera's case, a group of some 720 women are being studied to look for relationships between environmental exposures during pregnancy and long-term effects of the prenatal environment on their children, with an emphasis on preventing adverse health effects and later onset of adult disease.



Linked video:
Watch as Perera discusses her studies and the way that better understanding of gene and environment interactions can translate into strategies for prevention (06:20)
(Launches in new window)

Download Media Player:  Flash 

Perera has received numerous honors, including the Children's Environmental Health Excellence Award from the U.S. Environmental Protection Agency in 2005, and the Children's Environmental Health Network Award in 2008, for her pioneering work in molecular epidemiology in cancer as well as early life exposures.

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

[Return to Table of Contents](#)

Extramural papers of the month

By *Nancy Lamontagne*

- [Triclosan associated with liver damage in mice](#)
- [Potential treatment for Parkinson's targets mitochondrial dysfunction](#)
- [Biomonitoring studies should include phosphate flame retardants](#)
- [Killifish used to find genes that allow environmental adaptation](#)

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

Triclosan associated with liver damage in mice

NIEHS grantees report that mice with long-term exposure to the antibacterial agent triclosan experienced fibrosis and acceleration of cancer development in the liver. These findings add to earlier reports that this widely used antimicrobial agent can disrupt hormones and impair muscle contraction.

The researchers exposed mice to triclosan for six months, which equates to about 18 human years. The triclosan-treated mice exhibited cell proliferation, liver fibrosis, and proinflammatory responses that together form the type of environment within which human liver cancer forms. The researchers also chemically induced liver tumors in the mice and found that the mice exposed to triclosan had a large increase in tumor multiplicity, size, and incidence compared to unexposed mice. Findings from the study suggests that triclosan's negative effects on the liver may result from interference with the constitutive androstane receptor, which plays a role in clearing foreign chemicals from the body.

The authors recommend that because the findings strongly suggest there are adverse health effects in mice with long-term exposure, the relevance of triclosan liver toxicity to humans should be evaluated. They also pointed out that eliminating the use of triclosan in products that are high volume but low benefit, such as hand soaps, would help lessen exposure.

Citation: Yueh MF, Taniguchi K, Chen S, Evans RM, Hammock BD, Karin M, Tukey RH. 2014. The commonly used antimicrobial additive triclosan is a liver tumor promoter. Proc Natl Acad Sci U S A 111(48):17200-17205. (See [story](#).)

[Return to Table of Contents](#)

Potential treatment for Parkinson's targets mitochondrial dysfunction

Research supported in part by NIEHS showed that inhibiting a protein required for mitochondrial fission brought positive effects in experimental mouse models of Parkinson's disease. These findings could lead to a treatment that would target the neuronal mitochondrial dysfunction that is associated with Parkinson's.

Mitochondria frequently change shape, size, number, and location through the processes of fission and fusion. To determine whether targeting fission and fusion might have a therapeutic effect on Parkinson's, researchers used mice that model the mitochondrial impairments seen in the disease.

They found that targeting fission, which produces smaller and more motile mitochondria, was beneficial in the animal models studied. Fission requires the recruitment of the GTPase dynamin-related protein-1 (Drp1) from the cytosol to the outer mitochondrial membrane. By blocking Drp1 using gene-therapy or a chemical approach, the researchers reduced both cell death and the deficits in dopamine release, effectively reversing the Parkinson's disease process.

Citation: Rappold PM, Cui M, Grima JC, Fan RZ, de Mesy-Bentley KL, Chen L, Zhuang X, Bowers WJ, Tieu K. 2014. Drp1 inhibition attenuates neurotoxicity and dopamine release deficits in vivo. Nat Commun 5:5244.

[Return to Table of Contents](#)

Biomonitoring studies should include phosphate flame retardants

Based on their analysis of phosphate flame retardant (PFR) metabolite levels in people living in California, an NIEHS grantee and colleagues recommend that future biomonitoring studies include the six major metabolites of the most prominent PFRs.

PFR use is increasing as manufacturers seek replacements for the banned pentabromodiphenyl ether mixtures that were previously used as flame retardants. PFRs are detected at higher concentrations than other flame retardants found in house dust, but little is known about how house dust concentrations relate to biological levels. To find out more, the researchers analyzed urine samples from 16 California residents for the six expected major metabolites of the most prominent PFRs and qualitatively screened for 18 other metabolites predicted from *in vitro* studies. They also collected dust samples and information about home furniture from the participants.

Although this is the first known U.S. study to measure all six major PFR metabolites, the researchers detected the compounds at levels similar to those reported in previous European studies, although few comparisons are available. For many PFR combinations, metabolite levels were correlated, suggesting they commonly co-occur. Two of the metabolite-parent pairs studied showed weakly positive nonsignificant correlations between urine and dust samples. The researchers recommended including certain PFRs in future biomonitoring studies.

Citation: [Dodson RE, Van den Eede N, Covaci A, Perovich LJ, Brody JG, Rudel RA. 2014. Urinary biomonitoring of phosphate flame retardants: levels in California adults and recommendations for future studies. Environ Sci Technol 48\(23\):13625-13633.](#)

[Return to Table of Contents](#)

Killifish used to find genes that allow environmental adaptation

Research funded in part by NIEHS has identified genes and gene regulation processes that allow killifish to transform the function and structure of its freshwater gills for use in salt water. These findings provide insight into how genes might interact with the environment and evolve toward the development of traits that can more easily respond to environmental changes.

The researchers previously observed that killifish are more vulnerable to arsenic during changes in salinity. Since arsenic prevents killifish from shifting between freshwater and seawater, they reasoned that arsenic could be used to identify which genes orchestrate these changes. The researchers exposed killifish to arsenic while they were acclimating to various levels of salinity and found that the genes orchestrating the killifish response were maintained at precise levels. These results suggest strict regulatory control of these genes may be a general feature of plastic responses in other organisms.

The investigators also found that plasticity-enabling genes seem to be organized in unusually simple networks. Natural selection acts on these networks differently, depending on the degree of plasticity required. Thus, killifish living in stable environments have less precise regulatory control over plasticity-enabling genes than do killifish living in unstable environments.

Citation: [Shaw JR, Hampton TH, King BL, Whitehead A, Galvez F, Gross RH, Keith N, Notch E, Jung D, Glaholt SP, Chen CY, Colbourne JK, Stanton BA. 2014. Natural selection canalizes expression variation of environmentally induced plasticity-enabling genes. Mol Biol Evol 31\(11\):3002-3015.](#)

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

[Return to Table of Contents](#)

Intramural papers of the month

By Simone Otto, Jacqueline Powell, Deepa Singh, Shannon Whirlledge, and Qing Xu

- [NTP finds a better animal model to evaluate the effects of chemical exposure](#)
- [Time-lapse crystallography reveals link between oxidative stress and disease](#)
- [MED25 mediates epigenetic regulation of human drug metabolism gene CYP2C9](#)
- [Researchers find protein involved in glucocorticoid-resistant asthma](#)
- [Ambient air pollution increases the risk of asthma and wheeze in adult women](#)

NTP finds a better animal model to evaluate the effects of chemical exposure

Researchers from the National Toxicology Program used a genetically diverse mouse model to predict the range of toxicity that might be observed in humans after exposure to benzene, a common air pollutant and known human carcinogen. Using Diversity Outbred (DO) mice, the study estimated a benzene exposure threshold of 0.205 parts per million, which is consistent with observations of response in humans but is well below the value previously obtained using inbred mice. This study demonstrates the value of using a model, such as DO mice, that better reflects the genetic variability and range of response seen in human populations.

To evaluate the response to benzene, the scientists measured the frequency of micronucleated red blood cells in each genetically unique DO mouse, before and after inhalation exposure to benzene. Micronuclei are standard biomarkers of chromosomal damage. At the end of the 28-day exposure period, a reproducible, dose-dependent increase in benzene-induced chromosomal damage was observed. Importantly, a marked variation in response was seen among the mice, with some mice showing no increase in micronuclei and others showing large increases. Using genetic mapping and linkage analysis, the researchers identified a locus associated with resistance to benzene-induced genotoxicity on mouse chromosome 10. Sulfotransferases located in this region are likely candidate genes for benzene resistance. **(DS)**

Citation: French JE, Gatti DM, Morgan DL, Kissling GE, Shockley KR, Knudsen GA, Shepard KG, Price HC, King D, Witt KL, Pedersen LC, Munger SC, Svenson KL, Churchill GA. 2014. Diversity outbred mice identify population-based exposure thresholds and genetic factors that influence benzene-induced genotoxicity. *Environ Health Perspect* 122:711–718. [[Story](#)]

[Return to Table of Contents](#)

Time-lapse crystallography reveals link between oxidative stress and disease

NIEHS researchers and their collaborators have discovered how oxidative stress can lead to blocked DNA repair, which is implicated in many human diseases. For the first time, researchers were able to visualize how oxidized DNA nucleotides are incorporated during replication, and how a cell discriminates between damaged and undamaged substrates. These findings could lead to a better understanding of how DNA damage, stemming from environmental exposures, leads to diseases such as cancer.

Environmental chemicals, including air pollution, flame retardants, and phthalates, induce oxidative stress, which reflects an imbalance between damage and the body's ability to repair the damage. Oxidative stress can result in an accumulation of damaged DNA substrates that, when incorporated into DNA, results in DNA breaks, genomic instability, and disease.

Utilizing time-lapse crystallography, a method that allows the visualization of DNA synthesis over time, the researchers found that the incorporation of oxidized DNA substrates confounds later stages of DNA repair, which ultimately may lead to breaks in the DNA and cell death. Interestingly, cancerous cells are able to escape cell death in an environment with more oxidative stress by removing oxidized DNA substrates. Targeting the way cancer cells handle oxidative stress may lead to more effective treatments. **(SW)**

Citation: [Freudenthal BD, Beard WA, Perera L, Shock DD, Kim T, Schlick T, Wilson SH. 2014. Uncovering the polymerase-induced cytotoxicity of an oxidized nucleotide. Nature; doi:10.1038/nature13886 \[Online 17 November 2014\]. \[Story\]](#)

[Return to Table of Contents](#)

MED25 mediates epigenetic regulation of human drug metabolism gene CYP2C9

NIEHS researchers revealed that Mediator subunit MED25 dictates the status of histone H3K27 to regulate the expression of CYP2C9, which is one of the cytochrome P450 (CYP) enzymes that clear pharmaceutical compounds and other chemicals in the liver. The study delineates epigenetic mechanisms underlying regulation of CYP2C9 and other CYP genes.

MED25 is a component of Mediator complex that interacts with transcription factors and RNA polymerase II to initiate the transcription of target genes. Previous studies from the same group of scientists showed that transactivation of CYP2C9 involves association of MED25 with nuclear receptor HNF4alpha at corresponding promoter binding sites. In this paper, the researchers further dissected the role of MED25 in epigenetic regulation of CYP2C9 expression.

After overexpressing or silencing MED25 in HepG2 cells, the researchers found a MED25-dependent change in H3K27 modifications. In the presence of MED25, the HNF4alpha binding region of the CYP2C9 promoter was enriched with the activating marker H3K27ac and other coactivators that acetylate histone. MED25 also induced a permissive chromatin conformation that allowed increased gene expression. In contrast, absence of MED25 led to accumulation of the repressing marker H3K27me3 and recruitment of PRC2, which trimethylated H3K27 and suppressed expression. These results suggest an essential role of MED25 in activation of a number of HNF4alpha inducible genes. **(QX)**

Citation: [Englert NA, Luo G, Goldstein JA, Surapureddi S. 2014. Epigenetic modification of histone 3 lysine 27: Mediator subunit MED25 is required for the dissociation of Polycomb repressive complex 2 from the promoter of cytochrome P450 2C9. J Biol Chem; doi:10.1074/jbc.M114.579474 \[Online 12 November 2014\].](#)

[Return to Table of Contents](#)

Researchers find protein involved in glucocorticoid-resistant asthma

In an article published in *Mucosal Immunology*, NIEHS researchers revealed a novel mechanism that gives rise to a form of asthma dominated by neutrophilic inflammation. Neutrophilic asthma, unlike eosinophilic asthma, is resistant to standard treatment with inhaled glucocorticoids. It stems from lung dendritic cells expressing TIR-domain-containing adapter-inducing interferon-beta (TRIF) protein.

The scientists sensitized TRIF knockout mice to ovalbumin by allowing them to inhale this protein after mixing it with extracts of common house dust that contain lipopolysaccharide, a component of bacteria known to increase T helper 17 (Th17) cells. When subsequently challenged with aerosolized ovalbumin, the TRIF

knockout mice had fewer Th17 cells, fewer neutrophils, and less airway constriction compared with similarly treated wild-type mice. Furthermore, dendritic cells from lungs of the TRIF knockout mice expressed very little CD40 and poorly stimulated Th17 cell differentiation in cell culture.

The researchers' demonstration that the CD40-TRIF-Th17 pathway leads to neutrophilic asthma suggests that small molecules that inhibit this pathway might be effective for treating neutrophilic asthma, without adversely affecting other immune functions in the lungs. **(SO)**

Citation: Hsia BJ, Whitehead GS, Thomas SY, Nakano K, Gowdy KM, Aloor JJ, Nakano H, Cook DN. 2014. Trif-dependent induction of Th17 immunity by lung dendritic cells. *Mucosal Immunol* 8(1):186-197.

[Return to Table of Contents](#)

Ambient air pollution increases the risk of asthma and wheeze in adult women

NIEHS researchers and collaborators reported that long-term exposure to particulate matter less than 2.5 micrometers in diameter (PM 2.5) increases the risk of developing asthma and wheeze in adult women. Previous research was done primarily in children and demonstrated an association between air pollution and the development of childhood asthma. No studies in adults have examined exposure to PM 2.5.

Using PM 2.5 and nitrogen dioxide (NO₂) concentrations estimated in the Sister Study, a nationwide cohort study of more than 50,000 U.S. women, researchers examined how ambient air pollution was related to follow-up self-reports of wheeze, chronic cough, and doctor diagnosed asthma in women without baseline symptoms. PM 2.5 and NO₂ concentrations were estimated at participants' primary addresses at the time of study enrollment, and annual averages were then derived from a national network of air pollution monitoring stations. In addition to the associations with PM_{2.5}, there was evidence for an association of NO₂ with wheeze.

Because the maximum estimated participant exposure in this analysis was less than the current Environmental Protection Agency's National Ambient Air Quality Standard, these results suggest that respiratory effects can be seen at levels well below the current national standards. **(JP)**

Citation: Young MT, Sandler DP, DeRoo LA, Vedal S, Kaufman JD, London SJ. 2014. Ambient air pollution exposure and incident adult asthma in a nationwide cohort of U.S. women. *Am J Respir Crit Care Med* 190(8):914-921.

(Simone Otto, Ph.D., is an Intramural Research Training Award fellow in the NIEHS Ion Channel Physiology Group. Former NIEHS postdoctoral fellow Jacqueline Powell, Ph.D., is a former NIEHS postdoctoral fellow now working as a clinical research scientist. Deepa Singh, Ph.D., is a visiting fellow in the NIEHS Mechanisms of Mutation Group. Shannon Whirlledge, Ph.D., is a research fellow in the NIEHS Molecular Endocrinology Group. Qing Xu is a biologist in the NIEHS Metabolism, Genes, and Environment Group.)

[Return to Table of Contents](#)

Inside the Institute

The good, the bad, and the ugly of the blood-brain barrier

By Jordan St Charles

In his Big Picture, Small Talk seminar Dec. 9, David Miller, Ph.D., deputy chief of the Signal Transduction Laboratory, described how therapeutic drugs and other foreign chemicals move around the body.

A new seminar series

Big Picture, Small Talk is a new series organized by Abee Boyles, Ph.D., of the National Toxicology Program, and by a cross-divisional organizing committee with the goal of presenting NIEHS research in a format that is more accessible to nonspecialists. Previous talks were given by [John Schelp](#), Geoffrey Mueller, Ph.D., and [Richard Kwok](#), Ph.D., with topics ranging from allergies to epidemiology.

“Feedback from participants has been positive, with people consistently commenting that the talks increase their knowledge of the topic, and that they enjoy learning more about research conducted at the institute,” said Boyles.

How drugs travel through the body

Miller began his talk by defining pharmacology, the science of how drugs interact with the body. He explained that drugs move through the body using the circulatory system.

Ingested drugs enter the circulatory system through the small intestine, then travel to the liver, where they can be metabolized into different forms. “From the liver, many of these metabolites get dumped into the blood and distributed throughout the body,” said Miller.

The blood-brain barrier and research in the Intracellular Regulation Group

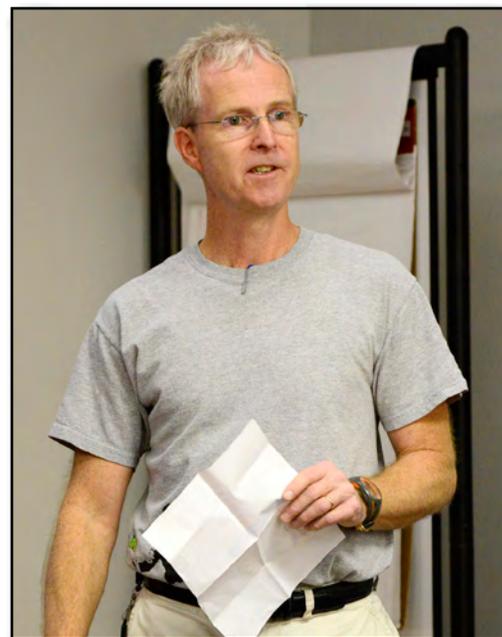
Certain tissues, such as the brain, placenta, and testes, have additional barriers to drugs. The brain is protected by a feature known as the blood-brain barrier. Blood entering the brain moves into small capillaries lined with endothelial cells, which Miller compared to a brick wall. There are plugs, called tight junctions, between the endothelial cells and transporters on the cell membranes. Efflux transporters recognize and block foreign chemicals.

Upcoming Big Picture, Small Talk

Big Spill, Small Talk: What Was in the Elk River Spill?

Scott Auerbach, Ph.D.,
National Toxicology Program

Tuesday, Jan. 20, 2015
1:00 – 2:00 p.m., Keystone 1003



Gary Bird, Ph.D., of the Signal Transduction Laboratory, introduced Miller, who joined NIEHS in 1985. (Photo courtesy of Steve McCaw)

Miller explained that in addition to keeping out dangerous chemicals, the blood-brain barrier may also keep out helpful drugs, such as chemotherapeutics. Research in Miller's lab focuses on finding ways to move drugs that have been shown to be effective in the test tube past the blood-brain barrier, so they can be effective in treating tumors in the brain.

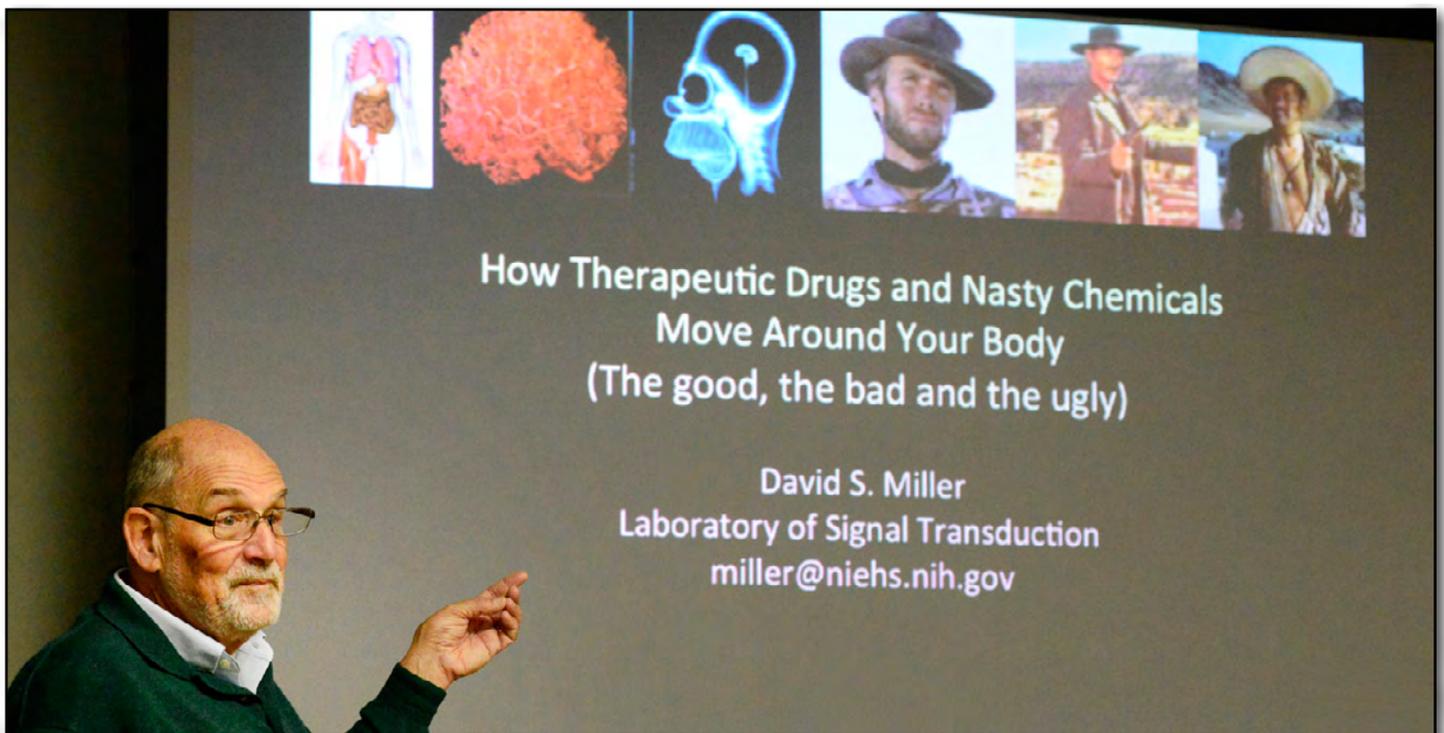
He showed several experiments featuring his favorite transporter, p-glycoprotein. In one experiment, the transporter was blocked with a drug called cyclosporine, which allowed chemotherapeutics to get across the barrier. Unfortunately, this method was only effective with levels of cyclosporine high enough to cause side effects.

To avoid these side effects, Miller's lab focuses on finding ways past the transporters by using cell-signaling molecules that would turn off the transporter. Patients would be treated with both a drug that signals the transporter to be turned off and a therapeutic drug, such as Taxol. "So by manipulating the dose and timing of the drug, I could create a time window when Taxol would go in, since the transporter is not working. But then the window would close, and the transporter would be there to protect the brain against other nasty things," he said, demonstrating the complexity of the challenges researchers face.

(Jordan St. Charles, Ph.D., is an Intramural Research and Training Award fellow in the DNA Replication Fidelity Group at NIEHS.)



Geoff Mueller, Ph.D., left, and Lars Pedersen, Ph.D., both of the Genome Integrity and Structural Biology Laboratory, pondered the difficulties of the blood-brain barrier. (Photo courtesy of Steve McCaw)



Miller spoke about pharmacology using many metaphors, including comparing his research to the movie "The Good, the Bad, and the Ugly." (Photo courtesy of Steve McCaw)

Volunteers from NIEHS wrap up outreach module at middle school

By Eddy Ball

Now entering its third year, the NIEHS Citizen Schools outreach program completed its latest module Dec. 11 at Lowes Grove Middle School in Durham, North Carolina, with an open house known as the WOW! event.

The open house is an opportunity for students to show off what they've learned during their apprenticeships to friends, family, and members of the community, as they celebrate the culmination of a ten-week interactive science education curriculum on Healthy Lungs, Happy Living.

With an emphasis on interactive learning, the program concluded its latest cycle with presentations by the middle school apprentices on lung capacity and the impact of pollution, by Team Breathers; the mechanism of breathing and lung physiology, by Team Exhalation; and a dramatic demonstration of the effect of cigarette smoking on lung health, by Team Living Lungs.

The exercises employed a hands-on, student-centered active learning approach to cultivate the participants' ability to make inquiries, and analyze and synthesize information.

Volunteers as citizen teachers

The outreach effort is coordinated by the NIEHS Office of Science Education and Diversity (OSD), directed by Ericka Reid, Ph.D., and staffed by NIEHS volunteer postdoctoral fellows and science and support staff (see [text box](#)). Working with Huei-Chen Lao, OSD K-12 science education and outreach coordinator, the NIEHS volunteers conceived, designed, revised, and presented the learning module.

"It's been a great program," Reid said. "We plan to stay involved with Citizen Schools with another module for next fall." The experience is valuable for students, but, as Reid noted, it also benefits volunteers, who thoroughly enjoy working with the students and value the opportunity to serve the community.

"I love the kids, and I wanted to give teachers some help," said volunteer Wanda Holliday, of the NIEHS Office of Acquisitions, about her first experience in the program. "The whole premise of Citizen Schools, getting citizens back involved in the community, is really important. They [the apprentices] benefit from getting involved with someone other than their teachers."



Team Breathers members demonstrated their lung capacity measurement apparatus to Holliday, left, and other visitors. (Photo courtesy of Steve McCaw)



One young apprentice acted out the physiology of breathing at the Team Exhalation demonstration. (Photo courtesy of Steve McCaw)

“It was important for me, as a first-time volunteer, that I had the support and encouragement of my supervisors at work and Citizen School team lead Huei-Chen Lao,” Holliday added. “I wouldn’t have been able to participate if they had not afforded me the time and the opportunity.”

Participating in the outreach effort can also help postdoctoral fellows expand their career goals. “A lot of the postdocs, when they come to us, they are looking for this kind of experience to add to their resumes,” Reid said, pointing to past volunteers who are now in scientific careers in outreach and education.

Celebrating its 20th year of service, [Citizen Schools](#) partners with public middle schools in low-income communities to provide an expanded learning day, by organizing volunteer professionals in a range of fields to enrich the educational experience for young learners. While NIEHS outreach modules have focused on basic science and public health, other modules in the Citizen Schools program at Lowes Grove included apprenticeships in electrical engineering, finance, tech startup, and Web design.



This colorful display contrasts graphically the difference between a healthy lung, right, and the lung of a longtime smoker, left, helping Team Living Lungs communicate its take-home message. (Photo courtesy of Steve McCaw)



Holliday, center, joined some of her students as the WOW! event came to a successful close. (Photo courtesy of Steve McCaw)



Leaders of the NIEHS and Citizen Schools effort said goodbye to the apprentices and looked forward to seeing each other again at Lowes Grove. Shown from left, are Citizen Schools teaching fellow Molly Wright, Lao, Citizen Schools teaching fellow Lauren Wolfe, Holliday, and Reid. (Photo courtesy of Steve McCaw)

A who's who of fall 2014 NIEHS Citizen Schools outreach

- Visiting fellow [Sara Andres, Ph.D.](#), of the Genome Stability Structural Biology Group
- Biologist [Kathleen Azzam, Ph.D.](#), of the Clinical Investigation of Host Defense Group
- Intramural Research Training Award (IRTA) fellow [Miranda Bernhardt, Ph.D.](#), of the Reproductive Medicine Group
- Head of the Comparative Medicine Branch Terry Blankenship-Paris, D.V.M.
- Visiting Fellow [Chun-Hsien Chu, Ph.D.](#), of the Neuropharmacology Group
- Wanda Holliday, of the Office of Acquisitions
- IRTA baccalaureate fellow [Palmyra Romeo](#), of the Synaptic and Developmental Plasticity Group
- Mary Waligora, of the Facilities Management Branch

NIEHS celebrates commitment to excellence

By Kelly Lenox

NIEHS celebrated 2014 staff achievements at a Dec. 12 awards ceremony focused on the theme “Commitment to Excellence.” NIEHS and National Toxicology Program (NTP) Director Linda Birnbaum, Ph.D., opened with a perspective from Dr. Martin Luther King Jr. — “All labor that uplifts humanity has dignity and importance and should be undertaken with painstaking excellence.”

“I think that’s what we do here at NIEHS,” said Birnbaum. “No matter what challenges come our way, we continue our work to uplift humanity, and we do it with a steadfast commitment to excellence.”

Gary Bird, Ph.D., staff scientist in the Calcium Regulation Group, emceed the ceremony and introduced the government and contract awardees. “It’s an honor and a pleasure,” he said.

Unsung Hero Awards — Ligon Perrow, A’tondra Carree, Debra Del Corral

Peer Recognition Awards — Clifton Baldwin, Anne Thompson, Kristen Fisher

Individual Merit Awards — Carol Shreffler, Mary Wolfe, Robin Mackar, Kimberly McAllister, Les Reinlib

Divisional Group Merit Awards

Division of Extramural Research and Training — Martha Barnes, Linda Bass, Gwen Collman, Kimberly Gray, Elizabeth McNair, Claudia Thompson, Beth Anderson, Jennifer Collins

Division of Intramural Research — Joel Abramowitz, Cynthia Arizona, Katherine Fine, Myra Westmoreland, Joan Packenham, Jane Lambert, Craig Wladyka, Edith Lee, Terry Lewis, Christine Philput

Cross-divisional Group Merit Awards

For exemplary leadership, management, and coordination of the Health Effects and Mitigation of Arsenic workshop — Beth Anderson, Maureen Avakian, Danielle Carlin, Justin Crane, Michelle Heacock, Heather Henry, Marisa Naujokas, Angie Sanders, William Suk, Erik Tokar, Michael Waalkes (see [story](#))



Bird donned a tuxedo for the ceremony, but didn’t let it interfere with the fun, showing doctored photographs of institute personnel among the awards. (Photo courtesy of Steve McCaw)



Clifton Baldwin, center, received a Peer Award for notable and extraordinary assistance to coworkers. Collman, left, and Birnbaum presented the award. (Photo courtesy of Steve McCaw)

For outstanding handling and completion of the NIEHS Division of Intramural Research reorganization — Joel Abramowitz, Cynthia Arizona, Robin Arnette, Catherine Boyd, Yvette Cobb, Nancy Delgais, Katherine Fine, Kristen Fisher, Christine Flowers, Cindy Garrard, Vanessa Howard, Susan Hart, Melissa Jones, Michelle Mayo, Nancy Mitchell, Barbara Morse, Ellen Moul, Joseph Poccia, William Schrader, Kent Stone, Cheryl Thompson, Myra Westmoreland

For exceptional organization and management of the NIEHS Clean Sweep — Kylie Brockenfelt, Kent Cameron, Trisha Castranio, Kenneth Coffey, Leslie Couch, Elizabeth Denholm, William Fitzgerald, Clyde Hasty, Ronald Herbert, Christopher Hunt, Paul Johnson, Paula Juras, John McLamb, Scott Merkle, Antares Nicklow, William Schrader, Valeria Shropshire, Carranza Smith, Michael Spencer, William Steinmetz, Thomas Steinbach, Mary Ellen Sutphin

For development and facilitation of the first Science, Teachers, and Research Summer (STaRS) Institute — Terry Blankenship-Paris, Christopher Campos, Kimberly Cannady, Ronald Cannon, Molly Cook, Joanne Damborsky, Matthew Edin, Lori Edwards, Neal Englert, Jennifer Fostel, George Fromm, Juhee Haam, Michael Humble, Huei-Chen Lao, Eric Milliman, Page Myers, Simone Otto, Robert Petrovich, Bart Phillips, Ericka Reid, Charles Romeo, Shepherd Schurman, Kevin Trotter, C.J. Tucker, Mitzie Walker, Shannon Whirlledge, Belinda Wilson (see [story](#))

For development of an NIEHS strategy to explore the role of mitochondria in the response to environmental exposures — David Balshaw, Lisa Chadwick, William Copeland, Astrid Haugen, Matthew Longley, Kimberly McAllister, Janine Santos, Daniel Shaughnessy, Fred Tyson, Leroy Worth

For developing and deploying the first Web-based Nonneoplastic Lesion Atlas — Amy Brix, Mark Cesta, Beth Bowden, Christine Flowers, Melvin Hamlin, Ronald Herbert, Sharon Hite, Robin Mackar, David Malarkey, Joseph Poccia, Robert Sills, Emily Singletary, Tom Steinbach, Cheryl Thompson, Mary Wolfe (see [story](#))

For exceptional teamwork and service in protecting the health of our employees and visitors — Kenneth Coffey, LINDIA ENGRAM, William Fitzgerald, Stavros Garantziotis, Clyde Hasty, Christopher Hunt, Paul Johnson, John McLamb, Scott Merkle, Valeria Shropshire, Carranza Smith, William Steinmetz

2014 highlights

Birnbaum highlighted the following achievements as progress toward the goal of working as “One NIEHS,” with better integration among divisions. “We’re sharing more, we’re collaborating more, and we’re leveraging our resources and expertise more,” she said.

- In 2014, 48 papers were authored by scientists from more than one NIEHS division.
- A successful [Science Days](#) event integrated both internal scientists and grantees.
- Cross-divisional faculty are collaborating on cutting-edge research topics including epigenetics, stem cell research, inflammation, predictive toxicology, the exposome, and global health.
- Every division is contributing to research on the Gulf oil spill, the West Virginia chemical spill, and establishment of the new NIH Disaster Research Response Project.
- There is more coordination between internal scientists and grantees, including more studies on bisphenol A.
- The [Big Picture, Small Talk](#) series is a homegrown, bottom-up program to allow those who aren’t scientists to get a better understanding of the work done at the institute, and for scientists to learn about other labs and programs.

For extraordinary effort in restoring services following the fire in the NIEHS data center — William Blair (ORF Contractor), Lynne Duncan, Amanda Dworaczyk, Brian Harris, Alison Hawkins, Matthew Jordan, Richard Little, Terrance Saulter, Joseph Shealey, James Stancil, Terry Wells, Mitch Williams, John Young

For exemplary teamwork and sustained effort in support of the 2014 NIEHS Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) site visit — William Blair, Terry Blankenship-Paris, Spencer Bridges, William Fitzgerald, Carlton (Buch) Gooch, Debbie Gaffney, Mary Grant, Alison Hawkins, Erika Hayes, Christopher Hunt, David Kurtz, Kathy Laber, Scott Merkle, Steve Parker, Charles Pearson, John Roberts, Larry Rogers, Brooke Rogerson, Susan Schnurr, Valeria Shropshire, Mary Waligora, Mitch Williams (see [story](#))

For sustained efforts and impactful contributions in assessing adverse health effects of exposure to inorganic arsenic — Darlene Dixon, Grace Kissling, Wei Qu, Erik Tokar, Michael Waalkes

For extraordinary planning, coordination, and execution of a successful communications plan for the NTP 13th Report on Carcinogens — Beth Bowden, Susan Dakin, Ella Darden, Miriam Gattis, Sanford Garner, Christine Flowers, Gloria Jahnke, Shawn Jeter, Ruth Lunn, Robin Mackar, Helen Rock, Diane Spencer, James Stojan, Cheryl Thompson, Anne Thompson, Yun Xie, Mary Wolfe (see [story](#))

Fellows Awards for Research Excellence (FARE) — Mallikarjuna Metukuri, Margaret Adgent, Sivapriya Ramamoorthy, Qingshan Wang, Natacha Steinckwich-Besancon, Matthew Quinn, Qing Cheng, Pengyi Yang, Barbara Nicol, Percy Tumbale, Quaker Harmon, Erica Ungewitter, Thuy-Ai Nguyen, Deirdre Tucker, Andrew Oldfield, Senthilkumar Cinghu, Georgia Alexander (see [story](#))



Elizabeth McMillan, center, received an Unsung Hero Award, for her professionalism in support of Division of Extramural Research and Training administration, from division director Gwen Collman, Ph.D., left, and Birnbaum. (Photo courtesy of Steve McCaw)



Another Unsung Hero, A'tondra Carree, second from right, was recognized for behind the scenes efforts to ensure accurate timekeeping and payroll for the institute. From left, Chris Long, deputy associate director for management, Joellen Austin, associate director for management, and Birnbaum presented the award. (Photo courtesy of Steve McCaw)



The Data Center Restoration Group received a Cross-divisional Group Merit Award from Birnbaum, for extraordinary effort in restoring much-needed services following a fire in the NIEHS data center. (Photo courtesy of Steve McCaw)



The Emergency Medical Response Team received a Cross-divisional Merit Award from Birnbaum, for exceptional teamwork and service in protecting the health of NIEHS employees and visitors. (Photo courtesy of Steve McCaw)

Sharing refreshments in the cafeteria after the ceremony provided further opportunities for cross-divisional cooperation. (Photo courtesy of Steve McCaw)



Birnbaum, right, presented a Cross-divisional Merit Award to the group responsible for exemplary teamwork and sustained effort in support of the 2014 AAALAC site visit. (Photo courtesy of Steve McCaw)

[Return to Table of Contents](#)



National Institute of
Environmental Health Sciences

The e-Factor, which is produced by the Office of Communications and Public Liaison, is the staff newsletter at the National Institute of Environmental Health Sciences. It is published as a communication service to NIEHS employees. We welcome your comments and suggestions. The content is not copyrighted. It can be downloaded and reprinted without permission. If you are an editor who wishes to use our material in your publication, we ask that you send us a copy for our records.

*Director of Communications: [Christine Bruske Flowers](#)
Editor-in-Chief: [Kelly Lenox](#) | Managing Editor: [Eddy Ball](#) | Science Editor: [Robin Arnette](#)*