

November 2015

## NIEHS Spotlight



### [Aziz Sancar and Paul Modrich share Nobel Prize in chemistry](#)

Sancar, a longtime NIEHS grantee, shared the chemistry prize with former NIEHS review board member Modrich, and with Tomas Lindahl.



### [New phase of breast cancer research focuses on prevention](#)

NIEHS and the National Cancer Institute announced a new phase of the Breast Cancer and the Environment Research Program, focused on prevention.



### [Burr gets an inside look at NIEHS](#)

U.S. Sen. Richard Burr visited NIEHS Oct. 15, getting a firsthand look at the institute and meeting with institute leadership.



### [Fellows turn training into faculty positions](#)

Three former NIEHS trainees have begun careers in academia, thanks in part to strong mentoring, as well as Pathway to Independence awards.



### [President's task force recommits to children's environmental health](#)

The President's Task Force on Environmental Health Risks and Safety Risks to Children reviewed progress and recommitted to achieving goals.

## Clinical Feature



### [Battling uterine fibroids](#)

Erica Marsh, M.D., a renowned uterine fibroid expert, spoke at NIEHS on the leading cause of hysterectomies in the United States.

## Science Notebook



### [Epigenetic studies improved by new software from NIEHS](#)

Software from NIEHS scientists will improve epigenetic research by providing a better method to correct DNA methylation data.



### [Jothi earns tenure from NIH](#)

Raja Jothi, Ph.D., lead researcher of the NIEHS Systems Biology Group was granted tenure from NIH in October.



### [Placental cadmium linked to increased risk of preeclampsia](#)

Cadmium levels in the placenta are associated with the risk of preeclampsia, according to an NIEHS-funded study published in PLOS ONE.



### [Test kits can motivate parents to reduce allergens](#)

NIEHS scientists report that in-home test kits, coupled with patient education, helped parents reduce allergen levels in their homes.

## NIEHS Spotlight



### [Worker Training Program builds collaborations and enhances data use](#)

WTP launched new grants with a workshop focused on boosting grantee collaborations and increasing data collection.



### [NIEHS and India meet at the intersection of climate change and health](#)

NIEHS and partners in India held a workshop to raise awareness and train public health researchers and professionals on the health impacts of climate change.



### [Roadmap for replacing rodents in acute toxicity tests](#)

Government, academic, and industry representatives moved forward with methods to reduce use of rodents in acute toxicity tests.

## Science Notebook



### [Variability among individuals spurs decision makers](#)

An NIEHS and National Academy of Sciences workshop addressed the role of interindividual variability in the regulation of pollutants.



### [Dolinoy receives NIH Transformative Research Award](#)

NIEHS grantee Dana Dolinoy, Ph.D., is one of eight winners of the National Institutes of Health award, for her innovative study of gene silencing.



### [NIEHS shines at Environmental Mutagenesis and Genomics Society meeting](#)

NIEHS scientists, fellows, and grantees stood out at the recent EMGS meeting, garnering several awards and continuing the society's tradition of mentorship.

## Inside the Institute



### [Schrader looks for bigger fish to fry in retirement](#)

NIEHS, along with friends and family, bade a fond farewell to Deputy Scientific Director Bill Schrader, Ph.D., upon his Sept. 30 retirement.



### [Lab retreat links NIEHS researchers, alumni, and collaborators](#)

The Genome Integrity and Structural Biology Laboratory held its first retreat, joining NIEHS scientists past and present with external collaborators and mentors.



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

The November issue of Environmental Health Perspectives examines weather-related mortality and new ways hospitals study disease outbreaks.

## Calendar of Upcoming Events

- **Nov. 4 (webinar)**, 11:00 a.m. – noon — In Vitro to In Vivo Extrapolation for High Throughput Prioritization and Decision Making webinar series featuring John Wambaugh, Ph.D., from the U.S. Environmental Protection Agency National Center for Computational Toxicology, speaking on “Building Fit-for-purpose Pharmacokinetic Models,” [register to attend](#)
- **Nov. 5-6**, Building 101, Rodbell Auditorium and mall area — NIEHS Science Days
- **Nov. 6 (Off-site event)**, Duke University Environmental Hall, noon – 1:30 p.m. — Duke University Integrated Toxicology and Environmental Health Program (ITEHP) Fall 2015 Seminar Series featuring Keith Cheng, M.D., Ph.D., from Penn State University, presenting “What is phenomics and how can it be used for society?”
- **Nov. 10**, Rodbell Auditorium, 11:00 a.m. – noon — Distinguished Lecture Seminar Series with Bert O’Malley, M.D., from Baylor College of Medicine discussing “Structure-Function Studies of the Estrogen Receptor-Coactivator Complex on DNA,” hosted by Ken Korach
- **Nov. 13 (Off-site event)**, Duke University Environmental Hall, Field Auditorium, 8:30 a.m. – 4:00 p.m. — ITEHP Fall 2015 Seminar Series Fall Symposium: The Toxicity of Power, [register to attend](#)
- **Nov. 19-20 (Off-site event)**, Arlington, Virginia — Society of Toxicology Future Tox III Bridges for Translation meeting “Transforming 21st Century Science into Risk Assessment and Regulatory Decision-Making”
- **Dec. 1-2**, Rodbell Auditorium, 8:30 a.m. – 5:00 p.m. — National Toxicology Program Board of Scientific Counselors meeting
- **Dec. 2-4 (Off-site event)**, Washington, D.C. — [Tribal Ecological Knowledge Workshop](#)
- View More Events: [NIEHS Public Calendar](#)

## Extramural Research

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

- [Exposure to phenols affects pubertal development in girls](#)
- [Recombinase enzymes recognize matching DNA three bases at a time](#)
- [Time between births associated with autism risk](#)
- [Faster measurements of brominated flame retardants](#)

## Intramural Research

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

- [NTP finds molecular differences between hepatoblastomas and hepatocellular carcinomas](#)
- [Mitochondrial POLG2 disease variants impair cellular energy production](#)
- [Transient metal ions mediate the direction of DNA synthesis](#)
- [The AF-2 domain of estrogen receptor alpha suppresses AF1](#)
- [Improved detection methods for environmental chemicals](#)

# NIEHS Spotlight

## Aziz Sancar and Paul Modrich share Nobel Prize in chemistry

By John Yewell

Aziz Sancar, M.D., Ph.D., a longtime NIEHS grantee, was named a winner of the 2015 Nobel Prize in chemistry. He shares the award with Paul Modrich, Ph.D., from Duke University School of Medicine and the Howard Hughes Medical Institute, and Tomas Lindahl, Ph.D., from the Francis Crick Institute and Clare Hall Laboratory in Great Britain. All three were honored for their work on the [mechanisms of DNA repair](#).

“I was very pleased to hear it,” Sancar told the Environmental Factor the day after getting the call from the Nobel committee. The award was also celebrated around the NIEHS campus. “We at NIEHS are thrilled to be able to support the vital work he is doing,” said Linda Birnbaum, Ph.D., director of NIEHS and the National Toxicology Program. “He is an extremely deserving candidate for the award.”



*Sancar's ability to generate knowledge about the molecular details of the process for repairing UV damage to DNA changed the entire research field, according to a [statement by the Royal Swedish Academy of Sciences](#). (Photo courtesy of Max Englund)*



**Linked Audio:**  
[Hear how Aziz Sancar reacted when he got the call that he has been awarded the 2015 Nobel Prize in Chemistry. \(3:20\)](#)

(Launches in new window)

Download Media Player:  Quicktime 

### Three approaches to studying DNA repair

[Sancar](#) is the Sarah Graham Kenan Professor of Biochemistry and Biophysics at the University of North Carolina at Chapel Hill School of Medicine (UNC). The Nobel committee honored Sancar for his work on two mechanisms that repair DNA damage. One mechanism involves the enzyme photolyase, which repairs the damage caused by ultraviolet (UV) light, which can cause skin cancer. The other is nucleotide excision, which repairs DNA strands damaged by carcinogenic substances, such as cigarette smoke and industrial pollution.

[Modrich](#) was recognized for his work recreating the molecular mechanism known as DNA mismatch repair, which corrects mismatched strands when DNA is copied. Modrich also has connections with NIEHS. He served on several review boards,



*Arnette, left, celebrated with Sancar, her former postdoc advisor, at UNC following the announcement of his receipt of the 2015 Nobel Prize in chemistry. (Photo courtesy of Laura Lindsey-Boltz)*

including an external panel that reviews the work of NIEHS researchers, the [Board of Scientific Counselors](#), from 1995 to 2000.

[Lindahl's](#) work led to the first understanding of the instability of DNA. Although stable enough to allow for evolutionary change, DNA inevitably undergoes mutation, and certain proteins are used to effect repairs.

### **NIEHS support for study of nucleotide excision**

In the last decade, NIEHS support of Sancar's work has amounted to more than \$1.6 million dollars. His current grant from NIEHS involves studying whether the removal of an oligonucleotide DNA fragment can lead to autoimmunity.

A prolific writer, Sancar has produced more than 350 scientific papers in his career. In May, Sancar and his team completed the monumental task of mapping the entire nucleotide excision repair system. "Out of six billion base pairs, pick out a spot and we'll tell you how it is repaired," he said.

Thomas Kunkel, Ph.D., principle investigator for the NIEHS DNA Replication Fidelity Group, remembers Sancar from way back. Kunkel joined NIEHS in 1982, the same year Sancar went to UNC, and they collaborated during the next six years.

"Aziz is a brilliant scientist whose exposure at a national and international level is primarily due to his prolific publication record, rather than attendance at meetings," Kunkel said. "It's particularly telling to win the Nobel Prize without spreading one's gospel by personal appearance." Kunkel added, "I know all three, and I'm thrilled for all of them."

### **A well-deserved honor, say colleagues**

Former colleagues were delighted at the news of Sancar's prize. Robin Arnette, Ph.D., science editor in the NIEHS Office of Communications and Public Liaison, worked as a postdoctoral researcher for Sancar from 2000 to 2002. "Aziz has trained scores of graduate students and postdocs at UNC," she said. "All of us are extremely proud of his accomplishment and grateful for his guidance and instruction."

Bennett Van Houten, Ph.D., who served at NIEHS from 1999 to 2008, was among Sancar's earliest postdoctoral fellows, joining his lab in 1984. Van Houten, also an NIEHS grantee studying DNA repair, is a professor of molecular oncology at the University of Pittsburgh and Carnegie Mellon University. "What makes him a scientist worthy of winning the Nobel Prize is his tremendous work ethic," Van Houten said. "He has the ability to synthesize a huge amount of literature, develop highly productive collaborations, and be fearless taking on any project."

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

## **From Turkey to North Carolina via Texas**

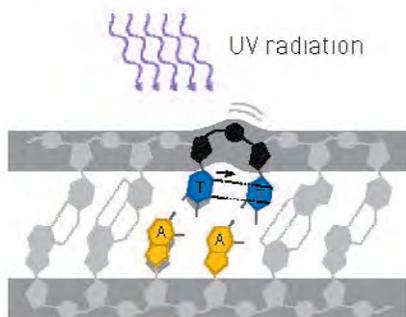
Sancar was born in 1946 in the small town of Savur, in the Mardin province in southeastern Turkey. He earned his M.D. at the University of Istanbul. In 1977, he earned his Ph.D. from the University of Texas at Dallas, working on photolyase, the photoreactivating enzyme of *E. coli*.

In 2005, Sancar was elected to the National Academy of Sciences as its first Turkish member, and in 2007 he won the Vehbi Koc award, known as the Turkish Nobel.

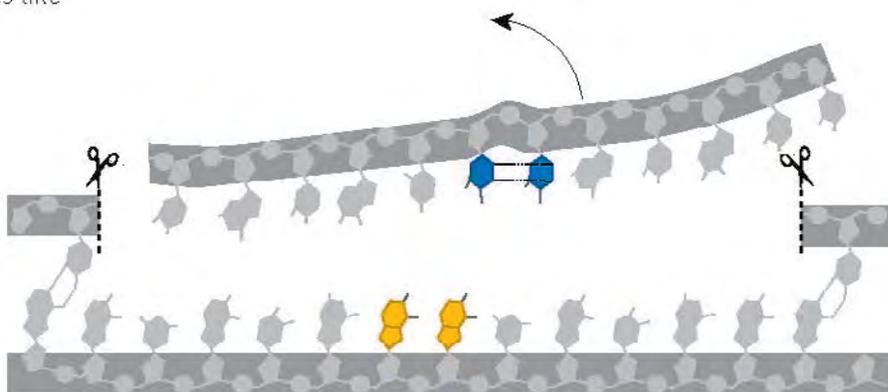
"I was well known in the Turkish scientific community," he said. "Now the man on the street knows me. That has changed my life."

## Nucleotide excision repair

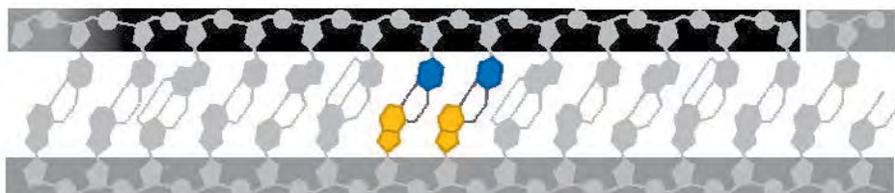
Nucleotide excision repairs DNA-injuries caused by UV radiation or carcinogenic substances like those found in cigarette smoke.



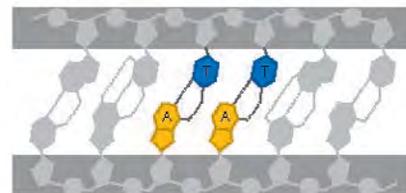
1 UV radiation can make two thymines bind to each other incorrectly.



2 The enzyme exonuclease finds the damage and cuts the DNA strand. Twelve nucleotides are removed.



3 DNA polymerase fills in the resulting gap.



4 DNA ligase seals the DNA strand. Now the injury has been dealt with.

Although Sancar considers his work on photolyase to be his most mechanistic and chemistry-related, he received the Nobel Prize in chemistry largely for his work on nucleotide excision repair, illustrated in this diagram from Royal Swedish Academy of Sciences. (Photo courtesy of the Royal Swedish Academy of Sciences)

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## New phase of breast cancer research focuses on prevention

By Virginia Guidry

A new phase of the [Breast Cancer and the Environment Research Program](#) (BCERP) will focus on prevention of the disease, according to an Oct. 8 announcement by NIEHS and the National Cancer Institute. Grant-funded researchers will now work across scientific disciplines, involve new racially and ethnically diverse communities, and expand the study of risk factors that precede breast cancer, such as breast density.

These new directions reflect recommendations made by the [Interagency Breast Cancer and Environmental Research Coordinating Committee](#) (IBCERCC) in 2013. The committee was congressionally mandated to review the state of the science around breast cancer and environmental influences by the Breast Cancer and Environmental Research Act of 2008.

## Broader focus, new partnerships

Recommendations included making prevention a priority, involving transdisciplinary research teams, engaging public stakeholders, collaborating across federal agencies, and communicating the science to the public. This broadened research focus will add to the growing knowledge of environmental and genetic factors that may influence breast cancer risk across the lifespan.

There are six new BCERP projects, plus a coordinating center to promote cross-project collaboration. All projects involve strong partnerships between researchers and organizations focused on breast cancer prevention or environmental health. Some projects are being conducted at more than one institution.

- Brigham and Women's Hospital, Boston  
Fox Chase Cancer Center, Philadelphia  
Silent Spring Institute, Newton, Massachusetts  
University of Chile, Santiago
- City of Hope-Beckman Research Institute, Duarte, California
- Columbia University Health Sciences, New York City
- Georgetown Lombardi Comprehensive Cancer Center, Washington, D.C.  
Uniformed Services University of the Health Sciences, Bethesda, Maryland
- Michigan State University, Lansing
- University of Massachusetts, Amherst  
Baystate Medical Center, Springfield, Massachusetts
- University of Wisconsin, Madison (Coordinating Center)

The focus on minority and socio-economically disadvantaged women is an important new step in addressing disparities in breast cancer outcomes. Although African-American women are diagnosed with breast cancer less often than white women, they experience higher prevalence of aggressive cancers and more deaths from the disease.

Another new direction for BCERP is research on the role of breast density as a possible intermediate risk factor for breast cancer. Dense breast tissue is one of the most common risk factors for breast cancer. Identifying links between environmental exposures and high breast density may provide new insights into prevention.

(Virginia Guidry, Ph.D., is a technical writer and public information specialist in the NIEHS Office of Communications and Public Liaison.)

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*"These priorities reflect our continued commitment to breast cancer prevention," noted Caroline Dilworth, Ph.D., BCERP program lead at NIEHS. "Our goal is to build on the high quality science we've been funding for more than a decade, while also being responsive to the expert recommendations of the IBCERCC report." (Photo courtesy of Steve McCaw)*



*"The beauty of this research is that scientific discoveries and community observations inform each other, in order to dive deeper into the complex causes of breast cancer," said Gwen Collman, Ph.D., director of the NIEHS Division of Extramural Research and Training. (Photo courtesy of Steve McCaw)*

# Burr gets an inside look at NIEHS

By Kelly Lenox

Richard Burr, U.S. senator for North Carolina, paid a visit Oct. 15 to NIEHS. He got a firsthand look at the institute, touring the facility and taking time to talk with NIEHS and National Toxicology Program Director Linda Birnbaum, Ph.D., and other members of the NIEHS leadership team.

In February, Birnbaum briefed the senator and his staff on Capitol Hill, but this was his first visit to the institute's campus in Research Triangle Park, North Carolina. "We were eager to show him how investment in biomedical research pays off in jobs and decreased health care costs," Birnbaum said.

"NIEHS research spans the range from basic biology, where we look at the mechanisms of how a disease like cancer is initiated or progresses, to applied toxicology and human epidemiology," Birnbaum told the senator. "NIEHS is unique at the NIH, because we are the only one whose research has a primary focus on preventing disease, rather than diagnosing and treating it."

## Innovation and partnerships

Throughout his visit, Burr displayed keen interest in the range of research, training, education, and other work conducted at the institute.

"The senator seemed to be particularly interested in knowing how the government can promote innovation in technology and healthcare," said Rick Woychik, Ph.D., deputy director of NIEHS, "especially when researchers in university laboratories, like those funded by NIEHS, engage in collaborative ventures with scientists in the private sector."

"He was really interested in our partnerships with local universities, both through the Clinical Research Unit, as well as our grants," agreed Mark Miller, Ph.D., who serves as Birnbaum's chief of staff.

According to Miller, Burr was impressed with the activities of the NIEHS Office of Science Education and Diversity, including its support of students and teachers through programs such as [Scholars Connect](#) and the two-week [Science, Teachers, and Research Summer \(STaRS\) Institute](#).



*The discussion during Burr's visit took note of National Breast Cancer Awareness Month. "Environmental factors are more readily identified and modified than genetic factors, and therefore present a tremendous opportunity to prevent breast cancer and other noncommunicable diseases," Birnbaum told the senator. (Photo courtesy of Steve McCaw)*



*At the CRU, Burr, left, learned about NIEHS clinical research studies from respiratory therapist Wayne Hughes, center, and Garantzotis. (Photo courtesy of Steve McCaw)*

During Birnbaum’s presentation, Burr received updates on other topics he is actively involved with, including past drinking water contamination at Camp Lejeune and Agent Orange exposures.

### Focus on Clinical Research Unit

Staff members at the NIEHS [Clinical Research Unit](#) (CRU) highlighted their interactions with the public and their efforts to recruit individuals from the local area to participate in biomedical research. Discussions touched on the CRU’s range of contributions, from studies at the individual level, to insights gained into the underlying principles of biology and their impacts on the nation’s broader public health.

Stavros Garantziotis, M.D., acting head of the Clinical Research Branch, showed Burr around the CRU. “We talked about the Environmental Polymorphisms Registry, the [Natural History of Asthma with Longitudinal Environmental Sampling](#) (NHALES) study, research on engineered nanomaterials, and the work of our [new recruit Dr. Natalie Shaw](#), suggesting that altered sleep patterns may affect the onset of puberty,” said Garantziotis.

Miller emphasized the advantages of the personal meeting and the information that was exchanged. “NIEHS doesn’t set policy,” he observed, “but when we can inform our representatives and senators about the science that we do, they’re better able to use that research to support the policy decisions that come before them.”

“I really enjoyed my visit today, and it’s been great to learn more about the institute’s work,” said Burr. “I’d like to come back soon to meet with NIEHS staff in a town hall format, so that everyone here has a chance to ask me questions.”



From left, Burr toured the NIEHS research labs, getting a firsthand view of the range of NIEHS research and other programs with Miller, Birnbaum, and Christine Flowers, director of the NIEHS Office of Communications and Public Liaison. “We have a commitment to conducting outreach, education, training, and supporting community partnerships, in addition to the highest quality, most rigorous laboratory-based science,” Birnbaum said. (Photo courtesy of Steve McCaw)

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# Fellows turn training into faculty positions

By Shannon Whirledge

This fall, three former NIEHS training fellows began new careers as assistant professors. Anne Marie Jukic, Ph.D., of the [Reproductive Epidemiology Group](#), headed by Allen Wilcox, M.D., Ph.D., is now an assistant professor at the Yale School of Public Health.

Bret Freudenthal, Ph.D., from the [DNA Repair and Nucleic Acid Enzymology Group](#), led by Sam Wilson, M.D., joined the University of Kansas Medical Center. Natalie Gassman, Ph.D., also from Wilson's group, was appointed assistant professor at the University of South Alabama Mitchell Cancer Institute.

## Outstanding mentoring is key

It is not surprising that these highly successful trainees came from laboratories headed by researchers who have recently received honors as Mentors of the Year (see related stories on [Wilson](#) and [Wilcox](#)). "My PI [principal investigator], my co-mentors, and my branch chief have been very supportive of my career," said Jukic.

"Wilson was instrumental in helping me prepare for an independent position," said Gassman. Freudenthal had similar praise for Wilson's career support. "[He] allowed me to be an equal peer in the work and establish a presence in the field," said Freudenthal. "This is reflective of the incredible person he is."

In addition to great support, all three fellows recognized the unique opportunities available to them at NIEHS. "The resources at NIEHS were instrumental in my growth and development during my fellowship," Freudenthal said.

While at the institute, all three participated in the annual career fair and a grant-writing workshop, as well as seminars on writing research statements, applying for academic jobs, and negotiating offers. Wilson said this training paid off. "Bret and Natalie have truly outstanding communications skills regarding scientific writing, oral presentations, and literature assessments," he noted.

## Steps to achieve independence

Part of these trainees' success stems from their recent National Institute of Health [Pathway to Independence](#) awards. "The single most important thing to do when transitioning from fellowship to academia is to write a grant," said Jukic. The process helps develop a research statement and lay out a trajectory for future research. "It [grant writing] forces you to consider how your research will grow, and that is invaluable when you are presenting your work and interviewing," said Gassman.



*"Try to learn from everyone around you, both peers and senior scientists," advised Jukic, "and from your mentors, in terms of how they work. You don't necessarily just want to complete a single paper or project, you want to learn how they practice science." (Photo courtesy of Steve McCaw)*



*"Try to do one activity a year that is outside your comfort zone and be honest with yourself about your goals," Freudenthal suggested. "Once you identify a career path, go after it and ask for mentorship." (Photo courtesy of Steve McCaw)*

Wilson feels his trainees are at the beginning of what will be outstanding careers. “I am confident Bret and Natalie will be leaders in their respective fields in the not too distant future,” he said. Wilcox also expressed great confidence in Jukic, who he notes is not only off to a great start in her career, but has already been an important role model and mentor to other trainees in the Epidemiology Branch.

Networking is often vital to a trainee’s successful job hunt. Freudenthal gives credit to his mother-in-law, whose networking skills helped him find out about the opening for his current position.

(Shannon Whirledge, Ph.D., is a research fellow in the NIEHS Laboratory of Signal Transduction.)

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*Speaking of Gassman, Wilson said, “One special contribution Natalie made to the group was her generous and steadfast diligence in promoting esprit de corps [team spirit].” (Photo courtesy of Steve McCaw)*

## President’s task force recommits to children’s environmental health

The President’s [Task Force](#) on Environmental Health Risks and Safety Risks to Children met Oct. 14 at the U.S. Department of Health and Human Services (HHS) in Washington, D.C., to review its accomplishments and recommit its members to continuing to work together to meet its goals.

President Bill Clinton established the task force in 1997, by Executive Order 13045. HHS Secretary Sylvia Burwell and U.S. Environmental Protection Agency Administrator Gina McCarthy, whose departments co-chair the task force, led the meeting of 17 federal agencies and offices.

### Key players from NIEHS

NIEHS and National Toxicology Program Director Linda Birnbaum, Ph.D., serves on the task force and spoke at the meeting. “The task force brings together federal agencies charged with ensuring children’s environmental health,” said Birnbaum, “and NIEHS has played, and will continue to play, a critical role in its efforts.”

John Bucher, Ph.D., director of the National Toxicology Program Division serves as chair of the Chemicals Subcommittee and Kimberly Thigpen Tart, J.D., program analyst in the NIEHS Office of Policy, Planning, and Evaluation serves as co-chair of the Climate Change Subcommittee. Both helped plan the meeting and also attended. Other NIEHS staff regularly contribute to the Task Force Steering Committee.



*McCarthy, left, and Burwell co-chair the task force, which considers ways to reduce a wide range of threats to children’s environmental health. (Photo courtesy of Chris Smith, HHS)*

## Achievements recognized

The task force integrates the activities of four subcommittees focused on asthma disparities, healthy settings, chemical risks, and climate change. Together, they work to accomplish the goals set out by the executive order, including:

- Identifying priority risks and issues.
- Developing strategies.
- Recommending and implementing interagency actions.
- Communicating information to decision makers for use in protecting children’s environmental health and safety.

Achievements of the task force include development of a [Coordinated Federal Action Plan to Reduce Racial and Ethnic Asthma Disparities](#). The action plan aims to reduce the burden of asthma in minority children and those with family incomes below the poverty level.

The task force also provided guidance to the Federal Healthy Homes Work Group in the development of its plan, [“Advancing Healthy Housing — A Strategy for Action.”](#)

Other achievements include identification of cross-agency biospecimen resources, to support measuring children’s chemical exposures, and consulting on the impacts of climate change on children’s environmental health, to inform a U.S. Global Change Research Program [Climate and Health Assessment](#).

A new work plan to guide the group’s efforts over the next year and into the future is in development and should be finalized by early next year.

## Ongoing and future efforts

Attendees at the meeting discussed ongoing and future efforts on children’s environmental health that would benefit from interagency coordination. Some of these efforts include:

- Communicating the risks of climate change to the public and the benefits of new pesticide regulations to teen workers.
- Exploring ways to encourage sustained funding for programs that address asthma disparities.
- Making use of new environmental monitoring and exposure data efforts to better characterize children’s health risks.



*The task force includes 17 federal agencies, and most were represented at the meeting. McCarthy and Burwell, center of front row, were flanked by Birnbaum, left of McCarthy; Bucher, behind McCarthy; Thigpen Tart, third from right; and John Balbus, M.D., NIEHS senior advisor for public health, back row, right. (Photo courtesy of DHHS)*

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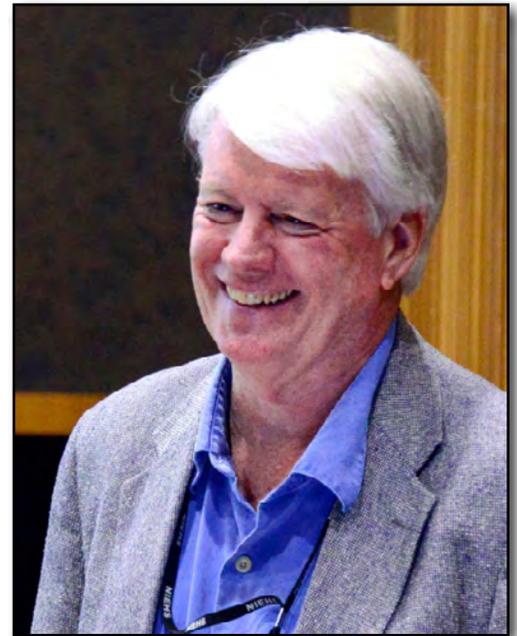
# Worker Training Program builds collaborations and enhances data use

By Tara Failey

The NIEHS Worker Training Program (WTP) launched a new round of grant awards with a Sept. 28-30 [awardee meeting and workshop](#). The event focused on improving collaborations and increasing the collection and use of training program data. Grantees represent a [network of nonprofit organizations](#) that provide training to workers who handle hazardous materials.

Awardees took advantage of the meeting to exchange training information, share program updates, and discover new areas of mutual interest. “Awardees have a variety of diverse resources they are bringing to the table,” said WTP Director [Joseph “Chip” Hughes](#) in his introduction.

NIEHS and National Toxicology Program Director Linda Birnbaum, Ph.D., gave the keynote address, emphasizing that WTP is at the forefront of worker training and response in the United States. Since the program launched in 1986, she said, nearly three million workers, have been trained in hazardous waste removal, HAZMAT disaster preparedness, and emergency response to major national disasters.



*Hughes, WTP director, oversees the programs to train workers to handle hazardous materials and waste, and perform emergency response. (Photo courtesy of Steve McCaw)*

## Data collection, evaluation, and collaboration

To enhance program evaluation, participants discussed collecting anecdotal information and using economic and outcome analyses to identify factors associated with success. [Sharon Beard](#), WTP industrial hygienist, pointed out how a program evaluation done for the Environmental Career Working Training Program showcased the [powerful economic impact](#) of the program.

Opportunities for additional collaboration were also discussed. Successful collaborations in the past included:

- Building relationships with state and local public health departments.
- Engaging with federal, regional, and local governments.
- Deepening partnerships between awardees.

## A sampling of conference presentations

“WTP as a National Response and Recovery Training Resource” — Charlene Obernauer, New York Committee for Occupational Safety and Health

“Public Health Meets HAZMAT: Bridging the Gap” — Linda Delp, Ph.D., Labor Occupational Safety and Health Program, University of California, Los Angeles

“Partnerships in Chicago” — Mollie Dowling, OAI Inc.

“Approaches to Assure Trainer Proficiency” — Carol Rice, Ph.D., Midwest Consortium for Hazardous Waste Worker Training at the University of Cincinnati

“WTP Data and Evaluation: Where to Go From Here” — Demia Wright, NIEHS WTP

Patricia Aldridge of the U.S. Department of Energy [HAMMER Federal Training Center](#) spoke to the importance of partnerships. “People working together can accomplish more than they can alone, and, as Aristotle famously stated, the whole is greater than the sum of its parts,” she said.

## Proving that training makes a difference

Ruth Ruttenberg, Ph.D., an evaluation consultant to many of the WTP awardees, encouraged grantees to measure their successes in protecting workers. She noted how collection of both data and stories contributes to demonstrating a program's importance. Useful stories document events that were prevented, as well as those that could have been avoided.

“For nearly three decades, workplace interventions made by way of WTP have helped prevent sicknesses and cancers among workers,” said Ruttenberg. “The NIEHS WTP program is living proof that training makes a difference.”

(Tara Failey is a communication specialist with MDB Inc., contractor for the NIEHS Division of Extramural Research and Training.)



*Wright, WTP public health educator, discussed evaluation of worker training programs. (Photo courtesy of Steve McCaw)*



*Birnbaum said that WTP has made great strides in improving public health in workplaces and communities since it began in 1986. (Photo courtesy of Steve McCaw)*



*George Tucker, head of the NIEHS Grants Management Branch, presented an overview of the grants process. (Photo courtesy of Steve McCaw)*



*Beard described the evaluation of the Environmental Career Working Training Program and encouraged awardees to use similar evaluation techniques. (Photo courtesy of Steve McCaw)*



*In addition to giving a presentation, Obernauer actively participated in discussions at the meeting. (Photo courtesy of Steve McCaw)*

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# NIEHS and India meet at the intersection of climate change and health

*By Bono Sen*

NIEHS collaborated with organizers in India to host a Sept. 22-24 training workshop, Understanding Climate and Health Associations in India (UCHAI). The event was held to raise awareness and train public health researchers and professionals on the health impacts of climate change.

Like many developing countries, India faces a disproportionate share of adverse impacts from climate change, which worsen its many public health challenges. The government of India has recognized health as a priority area in its climate adaptation strategy, and many states now include initiatives related to health in their climate action plans.

The organizers invited early career faculty, researchers, and others in the hope of expanding the number of experts who can assist in the country's adaptation efforts. The workshop, held in New Delhi, was organized by TARU Leading Edge, an Indian consulting firm focused on climate change and disaster risk reduction, and the [NIEHS-WHO Collaborating Centre for Environmental Health Sciences](#), in partnership with the Indian Meteorological Society.

## A critical challenge for environmental health

The opening speech was given by Soumya Swaminathan, M.D., secretary of the Department of Health Research in India's Ministry of Health and Family Welfare and director general for the Indian Council of Medical Research. She noted that climate change will emerge as a critical challenge for environmental health in India, in addition to existing issues such as water and sanitation.

In his keynote address, John Balbus, M.D., NIEHS senior advisor for public health and director of the NIEHS-WHO Collaborating Centre, emphasized the need to conduct local research, and then find ways to effectively communicate the results to different stakeholders. "This will be important to inform health policies and action on the ground," he said.



*Swaminathan, center, and other participants looked on as Balbus, right, participated in the lamp lighting ceremony that is traditionally performed before important events and during daily worship. The light symbolizes knowledge, which is considered to be the greatest wealth in life. (Photo courtesy of Nitish Dogra)*



*Participants in the workshop included, from left, Pramod Deshmukh, from Sansdkriti Samvardhan Mandal, a nongovernmental organization working on sustainable agriculture; Manu Prakash, director and practice head of policy and public services at TARU; Sen; Dogra; Balbus; Smriti Trikha, Ph.D., senior science manager for the Indo-US Science and Technology Forum; Juli Trtanj, from the National Oceanographic and Atmospheric Administration; and Diya Dutt, Ph.D., deputy director of the United States-India Educational Foundation. (Photo courtesy of Nitish Dogra)*

Also discussed was the importance of community-based participatory research, in particular, the need to engage community stakeholders in research design, project implementation, communication of findings, and the decision-making process.



## Building a community of practice

The workshop was a first step in developing a network, or community of practice, focused on three core frameworks — vulnerability, adaptation, and cobenefits of efforts to reduce climate change. The event delivered a mix of technical lectures, case studies, and training exercises to the audience drawn from India’s health, water, agriculture, transport, energy, and urban planning sectors.

Participants also visited the India Meteorological Department, observing use of climate and weather data and state-of-the-art computing technologies for health protection.

Looking ahead, the network’s aim is to help India build resilience in its health sector. Planned activities include training, facilitating local research, and developing early warning systems and health-related action plans. Through both domestic and Indo-U.S. collaborations, the organizers hope that the community of practice will play a central role in raising awareness about climate change and health issues.

“I have been able to translate my own learning into convening the most extensive, systematic training effort at the national level in India,” said Nitish Dogra, M.D., an advisor from TARU and former Fulbright-Nehru Environmental Leadership Program Fellow at Johns Hopkins University in Baltimore. “UCHAI, meaning peak in Hindi, India’s official language, undoubtedly represents a new peak in capacity building at the intersection of climate change and public health in India.”

(Bono Sen, Ph.D., is a program coordinator for the NIEHS Global Environmental Health program and was one of the workshop planners.)

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## Roadmap for replacing rodents in acute toxicity tests

*By Catherine Sprankle*

Attendees at a recent workshop agreed on plans to advance methods for product safety testing that meet the needs of regulatory agencies while reducing the use of rodents.

Representatives from government agencies, academia, and industry gathered at a Sept. 24-25 workshop co-organized by the National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM; see [sidebar](#)). The workshop, [Alternative Approaches for Identifying Acute Systemic Toxicity: Moving from Research to Regulatory Testing](#), was held at the National Institutes of Health in Bethesda, Maryland. Other organizers included PETA International Science Consortium Ltd. (PISC) and Physicians Committee for Responsible Medicine (PCRM).

### New options for preventing poisoning

[Acute systemic toxicity tests](#) measure the potential of chemicals to cause illness shortly after being swallowed, inhaled, or absorbed through the skin. Data from these tests are used to develop warning labels for packaging of products containing these chemicals and recommendations for personal protection when handling them.

Acute systemic toxicity tests typically involve rodents, but alternatives using high-throughput and computational methods have the potential to identify human toxicity more quickly, using fewer animals.

Representatives of U.S. regulatory agencies opened the workshop by reviewing the acute toxicity data that they require and how they use it. Speakers from industries and academia then presented case studies of how computational methods and tests using fish embryos have been used to assess pesticide toxicity.

### Research needs and next steps

During breakout discussion sessions, participants identified the resources needed for moving forward. One such need is the collection and curation of high-quality reference data. This data, from previous rodent tests, will be used to evaluate the new approaches. Attendees emphasized the importance of characterizing the variability in this reference data. Scientists at NTP and NICEATM will take the lead in coordinating collection of reference data from sources identified during the workshop.

Other needs included training on use and interpretation of computational approaches, and global consistency in testing requirements.

Each breakout group crafted a roadmap and strategy for reducing or replacing rodent use within a three-year timeframe. The strategies will be implemented by a new working group, composed of workshop participants and supported by NICEATM. The workshop proceedings will be submitted for publication early next year.

(Catherine Sprankle is a communications specialist for ILS, the contractor supporting NICEATM.)



*Participants appreciated the opportunity to hear from regulatory agency representatives including, from left, panelists Elissa Reaves, Ph.D., from the U.S. Environmental Protection Agency (EPA); Joanna Matheson, Ph.D., from the U.S. Consumer Product Safety Commission; and Louis Scarano, Ph.D., from EPA. (Photo courtesy of Ashley Somawang, PCRM)*

### Finding alternatives to animal testing

The term alternative methods refers to methods of research and testing that use fewer or no animals, or that reduce animal pain and distress.

NICEATM is an office within the NTP that supports NTP high-throughput screening projects and development of novel approaches to testing. Integrated Laboratory Systems Inc. (ILS) supports these activities.



*Co-organizers of the workshop included, from left, Jon Hamm, Ph.D., from ILS; Amy Clippinger, Ph.D., from PISC; Kristie Sullivan from PCRM, and David Allen, Ph.D., from ILS. (Photo courtesy of Ashley Somawang, PCRM)*



*The approximately 60 workshop attendees discussed national and international regulatory requirements for acute systemic toxicity testing and considered recent case studies of using nonanimal approaches for this testing. (Photo courtesy of Ashley Somawang, PCRM)*

## NICEATM activities prominent at recent meeting

At the Oct. 1-2 annual meeting of the American Society of Cellular and Computational Toxicology (ASCCT), held at EPA in Research Triangle Park, NICEATM and NTP activities in areas other than acute toxicity testing were highlighted. NICEATM director Warren Casey, Ph.D., reviewed motivations for developing new testing approaches. Other presenters included:

- Joanna Matheson, Ph.D. and Judy Strickland, Ph.D., from ILS, described an approach using computational methods and data from nonanimal tests to [identify substances that can cause allergic contact dermatitis](#).
- David Dix, Ph.D., from EPA, presented an approach developed in collaboration with NICEATM that could partially replace animal testing [required by the Endocrine Disruptor Screening Program](#).
- Ashley DeCoux, Ph.D., from PISC, described a study of the induction of pulmonary fibrosis by inhalation of carbon-based nanomaterials, a project that arose from a [February 2015 workshop co-organized by NICEATM](#).
- NICEATM and NTP scientists co-authored five posters on computational methods and reference databases for development of alternative testing approaches.
- The poster by Nicole Kleinstreuer, Ph.D., from ILS, “Identifying Reference Chemicals for Androgen Receptor Activity,” received the Edward Carney Predictive Toxicology Award, which is given to the first author of the best poster presented at the ASCCT annual meeting.

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# Clinical Feature

## Battling uterine fibroids

By Tara Ann Cartwright

Uterine leiomyomas, also known as fibroids, are the leading cause of hysterectomies in the United States and account for up to an estimated \$34 billion annually in costs.

On Oct. 10, Erica Marsh, M.D., a renowned uterine fibroid expert, addressed NIEHS scientists in her seminar, “‘There Will be Blood’: A Patient-centered View of Uterine Leiomyomas.” Marsh’s talk was hosted by NIEHS researcher Janet Hall, M.D.

### Origins unclear

According to Marsh, 65-70 percent of women have uterine fibroids by the age of 50, yet the origin of uterine fibroids remains unknown. She suggested that research and clinical experience have implicated several factors in fibroid development and growth, including race, obesity, genetics, and hormones such as estrogen and progesterone.

Marsh said that women often suffer for years before seeking medical treatment to relieve their symptoms. She advocated for greater attention by researchers and more public health outreach. “There is a lot of work to be done, and I hope some of you will engage in it,” she told the packed room.

### The impact of a fibroid diagnosis

Marsh, an assistant professor at Northwestern University Feinberg School of Medicine, and her team have qualitatively assessed the burden of uterine fibroids on women’s emotional health. Of the 60 women with symptomatic uterine fibroids recruited for her study, including African-Americans, Caucasians, Hispanics, and Asians, the majority exhibited a significant emotional response, including fear, anxiety, anger, and depression.

Many women also felt helpless and believed that they had no control over their fibroids. The title of her talk came from a comment by one patient who, discussing the variability of symptoms, said, “I know one thing — there will be blood.”



Marsh, left, shown with Hall, is a gynecologist, consultant, researcher, and lecturer on women’s health. She is a researcher on a national study that examines treatment outcomes in women who have fibroids. (Photo courtesy of Steve McCaw)

### What are uterine fibroids?

Marsh said that as many as 30 to 50 percent of women who have uterine fibroids, or leiomyomas, have symptoms. In many cases, they exhibit multiple clinical symptoms that vary with size and location. In general, leiomyomas:

- Are easily identifiable benign smooth muscle tumors of the uterus.
- Range in size from microscopic to bulky masses.
- Can be single or multiple masses.

Symptoms include:

- Heavy menstrual bleeding.
- Prolonged menstrual periods.
- Pelvic pressure or pain.
- Frequent urination or constipation.
- Painful intercourse.

## **Nutritional factors**

Ultrasound studies have demonstrated that African-American women exhibit a higher fibroid incidence than Caucasian women. This prevalence is driven by an earlier age of initiation and a longer growth window. Moreover, said Marsh, African-American women are more likely to be deficient in vitamin D than Caucasian women.

She cited several studies by [Donna Baird, Ph.D.](#), lead researcher in the NIEHS Epidemiology Branch. For instance, Baird's work has provided evidence that sufficient vitamin D may be associated with a reduced risk of uterine fibroids.

## **Racial disparities and health inequities**

The remainder of Marsh's presentation focused on racial disparities and health inequities, including the fact that women are more likely to face health inequities because their biological makeup demands more care and attention. "We need to do better for women," Marsh emphasized.

She and her team have found that African-American women often exhibit larger fibroids, which entail different treatment options and risks. Disparities in prevalence and treatment may lead not only to an altered perception of what is normal, but also to different recovery scenarios and greater dissatisfaction with care and treatment. "If all of your sisters have this experience, and your mother and aunts have this experience, you start to think this is normal," Marsh said.

A diagnosis of uterine fibroids is not something women should accept without diligent examination of lifestyle and options, she stressed. There are many approaches to treating uterine fibroids, including medications, hysterectomy, myomectomy, uterine artery embolization, and MRI-guided focused ultrasound surgery.

The patient and doctor must choose a treatment based on preferences, reproductive plans, and other medical considerations. Perhaps more importantly, new and effective therapies for this chronic condition must be developed. "I hope that I have convinced at least some of you to drop what you're doing immediately and look at uterine fibroids," she said. "We're talking about a serious public health issue."

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

### *Citations:*

[Ghant MS, Sengoba KS, Recht H, Cameron KA, Lawson AK, Marsh EE](#). 2015. Beyond the physical: a qualitative assessment of the burden of symptomatic uterine fibroids on women's emotional and psychosocial health. *J Psychosom Res.* 78(5):499-503.

[Baird DD, Hill MC, Schectman JM, Hollis BW](#). 2013. Vitamin d and the risk of uterine fibroids. *Epidemiology.* 24(3):447-453.

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# Science Notebook

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## Epigenetic studies improved by new software from NIEHS

By Kelly Lenox

An NIEHS team has developed a new tool to improve epigenetic studies that examine DNA methylation, which is a factor that affects how DNA functions. In a paper published Sept. 17 in the journal *Nucleic Acids Research*, the scientists introduced a novel method for correcting background noise in data from DNA methylation studies.

The researchers showed that the new tool, named ENmix (see [textbox](#)), outperformed other commonly used methods, and they have made the tool available in a user-friendly and freely available software package. By improving epigenetic research, ENmix may help researchers make new insights into the origins of common diseases.

### Important difference or background noise?

DNA methylation is a kind of epigenetic change, which means that rather than altering the underlying DNA, it instead affects when genes turn on and off. Epigenome-wide association studies (EWAS) play a key role in the search for links between epigenetic changes and disease. “Complex diseases can be associated with very small differences in DNA methylation profiles,” the authors wrote. Such small differences can be difficult to distinguish from the variability, or background noise, that may be caused by the measurement system used.

The authors said that the measurements of a tool commonly used in EWAS, the Illumina HumanMethylation450 BeadChip, can be affected by many experimental factors. Measurements that result from technical variations rather than useful information, and which generally cannot be reproduced, are known as background noise. Preprocessing the data to remove background noise is an important early step.

“We developed the ENmix background correction method in response to our own research need,” said [Jack Taylor, M.D., Ph.D.](#), senior researcher on the team and head of the NIEHS Molecular and Genetic Epidemiology Group. “We have looked at epigenetic change in relation to a variety of diseases, including breast cancer and cleft lip; exposures, such as DES [diethylstilbestrol], genistein, and smoking; and life course, or age. Most involve only small alterations in methylation, so it’s important that the methylation signal be measured accurately and precisely.”

### Limitations spark innovation

Zongli Xu, Ph.D., the paper’s lead author and a staff scientist in Taylor’s group, said that existing background correction methods for methylation data had a number of limitations and did not work particularly well. “Either they simply subtracted a fixed amount, or they were based on assumptions about data distributions that do not match those observed in methylation data,” he said.



*“The motivation for developing this tool set was to facilitate analysis of our own methylation data,” said Taylor. “We made the tools publicly available in the hope that other investigators will find them useful and gain better insight into associations between epigenetic changes, disease, and exposure.”*  
(Photo courtesy of Steve McCaw)

To develop the software package, Taylor and Xu collaborated with [Leping Li, Ph.D.](#), a lead researcher in the NIEHS Biostatistics and Computational Biology Branch, as well as Liang Niu, Ph.D., a research fellow in Li's group.

“Zongli and his colleagues weren't content to make do with the technical shortcomings associated with existing approaches,” said [Dale Sandler, Ph.D.](#), head of the NIEHS Epidemiology Branch. “Instead, they developed an innovative solution that will benefit other labs working on DNA methylation.”

### Greater precision improves methylation studies

The research team demonstrated that ENmix was more accurate and more reproducible than commonly used background subtraction methods. They also showed that the tool substantially reduced technical variations introduced by two different probe designs on the array.

Furthermore, the researchers showed that using ENmix can improve identification of novel disease-associated methylation sites and result in smaller estimates of margins of error.

“We note in particular that ENmix\_est [one component of the software suite] has application for the analysis of publically available methylation data sets where background intensity data are not available,” the authors said.

*Citation:* [Xu Z, Niu L, Li L, Taylor JA](#). 2015. ENmix: a novel background correction method for Illumina HumanMethylation450 BeadChip. *Nucleic Acids Res.* doi:10.1093/nar/gkv907. [Online 17 Sept. 2015]



*Xu said that ENmix provides a set of flexible and transparent tools for preprocessing EWAS data in a package that is both computationally efficient and user-friendly. (Photo courtesy of Zongli Xu)*

## ENmix at a glance

ENmix includes a suite of tools in addition to background correction, said Xu. These tools, which are part of the free package available on the [Bioconductor website](#), allow users to:

- Visualize quality control data in several ways.
- Filter out low-quality samples and probes.
- Identify and filter outliers.
- Plot data distributions accurately and quickly.
- Account for missing data.
- Normalize data across arrays.
- Identify probes with unusual distributions.
- Explore confounding variables for EWAS analysis.

ENmix is designed to support large-scale data analysis by providing efficient parallel computing wrappers for the functions listed above, as well as other techniques for probe bias and batch correction.

The software is compatible with several related R packages, and the component functions can be easily incorporated into some existing analysis pipelines.

# Jothi earns tenure from NIH

*By Ian Thomas*

When Raja Jothi, Ph.D., arrived at the National Institutes of Health (NIH) in Bethesda, Maryland, in 2004, he was determined to put his computational skills to work, to make a difference in biomedical sciences. In 2009, that goal came into sharper focus when he shifted gears to a tenure-track research position at NIEHS.

Now lead researcher of the Systems Biology Group in the NIEHS Laboratory of Epigenetics and Stem Cell Biology, Jothi was granted tenure status from NIH in October. “It is always good to know that you are doing good work,” said Jothi. “Tenure gives us the freedom to take on bigger challenges and risks.”

“A lot of people helped me to get here,” he continued, “from my mentors and colleagues to my trainees, who ran the gauntlet during my formative years as an independent researcher, and very few, if any, of my successes would have been possible without them.”



*When he is not in the lab, Jothi enjoys spending time with family and following the Dallas Cowboys. (Photo courtesy of Steve McCaw)*

## The road so far

A native of Chennai, India, Jothi began his education at the University of Madras in Chennai, where he earned a bachelors degree in computer science and engineering. He then attended graduate school at the University of Texas at Dallas, where he completed masters and doctoral degrees in the same fields.

After his time in Texas, Jothi made the trek to NIH. There he served as a postdoctoral research fellow in the Computational Biology Branch at the National Center for Biotechnology Information, and then in the Laboratory of Molecular Immunology at the National Heart, Lung, and Blood Institute.

In the years since, Jothi has served on the editorial boards of the journals PLOS ONE and Frontiers in Bioinformatics and Computational Biology. He is also a member of the International Society for Computational Biology.

## By the numbers

At NIEHS, the Jothi lab seeks to understand how transcription regulators, which are proteins that determine which genes are turned on or off, control gene expression programs during cellular development, differentiation, and disease development. His team uses embryonic stem cells as a model system to study gene networks that control key cell fate decisions.

Research within the group is largely data-driven, using computational analyses of published and in-house datasets from high-throughput genomic and proteomic studies, with the goal of generating testable hypotheses. The lab is used to test those hypotheses, and to perform biochemical experiments for gaining mechanistic insights.

“We have successfully identified and characterized many genes and pathways with previously unknown roles in embryonic stem cell biology,” Jothi explained. “Our current efforts include understanding how signaling cascades instruct epigenetic and transcription networks regulating cell fate decisions.”

(Ian Thomas is a public affairs specialist with the NIEHS Office of Communications and Public Liaison, and a regular contributor to the Environmental Factor.)

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# Placental cadmium linked to increased risk of preeclampsia

By Sarah Mishamandani and Carol Kelly

Cadmium levels in the placenta during pregnancy are associated with the risk of developing preeclampsia, according to a recent NIEHS-funded study from the University of North Carolina at Chapel Hill (UNC) Superfund Research Program (SRP) Center.

Preeclampsia during pregnancy is associated with high blood pressure and high levels of protein in the urine. It may contribute to the development of later-life cardiovascular disease and chronic kidney disease in the child. If untreated, it can also lead to an onset of seizures that pose a serious threat to the mother and baby.

The researchers, led by metals toxicologist Rebecca Fry, Ph.D., an associate professor at the UNC Gillings School of Global Public Health, also looked at the interactions between the mother's level of cadmium, a toxic metal, and the essential metals selenium and zinc. They found that selenium and zinc may play a role in protecting against cadmium-associated preeclampsia.

This study, published in the journal PLOS ONE, is the first to address the interactions among cadmium, essential metals in the placenta, and the odds of developing preeclampsia in pregnant women. People can be exposed to cadmium from cigarette smoke, contaminated air from facilities that burn fossil fuels, and some foods.

## Measuring metals in the placenta

Researchers selected 172 subjects with and without preeclampsia for a case-control study from the larger Maternal Oral Therapy to Reduce Obstetric Risk (MOTOR) study at UNC, which recruited pregnant women from the southeastern United States. Researchers used sensitive trace metals analysis to measure levels of cadmium, selenium, and zinc in placental tissue obtained after delivery. The range of concentrations of cadmium in the study was consistent with levels generally found in the U.S. and globally.

The scientists found that placental cadmium levels were significantly associated with preeclampsia. This relationship changed when they analyzed it in the context of selenium and zinc levels. Lower levels of zinc and selenium increased the odds for preeclampsia compared with the odds based on high cadmium levels alone. According to the authors, the findings suggest that zinc and selenium may play a role in protecting pregnant women from cadmium-associated preeclampsia.



*Fry's lab studies how environmental exposures are associated with human disease, with a particular focus on genomic and epigenomic factors. (Photo courtesy of Rebecca Fry)*

## Fry takes new role at UNC SRP Center

Fry was recently selected as the [new director of the UNC SRP Center](#). The center works to understand and reduce human and environmental health risks associated with high priority chemicals found at Superfund sites.

“In North Carolina and nationally, we are faced with serious environmental issues that need to be tackled with diverse interdisciplinary teams,” Fry said.

“I am excited to lead our group, with a mission to employ advanced risk analysis to protect populations at risk from these environmental harms.”

“These data support a critical public health issue — namely, that prenatal exposure to toxic metals has the potential to harm pregnancies,” said Fry. “The data also suggest that studying the interaction between these metals may be more biologically relevant than studying single metals alone. Our next steps are to understand the biological mechanisms that underlie the identified risk associations in humans, using systems toxicology and cell culture-based tools.”

## Epigenetics and preeclampsia

The precise trigger for preeclampsia is unknown, but it has been linked to impaired blood vessels in the placenta, a condition known as poor placentation. In a step toward understanding its cause, Fry led a study to identify epigenetic changes associated with the disease.

Her lab discovered that a decrease in CpG methylation, a type of epigenetic change that can change how DNA is expressed, altered the action of genes in the pathway that produces transforming growth factor-beta, a substance that controls cellular function. This alteration in genetic programming may be a major contributor to preeclampsia.

### *Citations:*

Laine JE, Ray P, Bodnar W, Cable PH, Boggess K, Offenbacher S, Fry RC. 2015. Placental cadmium levels are associated with increased preeclampsia risk. *PLoS One* 10(9): e0139341.

Martin E, Ray PD, Smeester L, Grace MR, Boggess K, Fry RC. 2015. Epigenetics and preeclampsia: defining functional epimutations in the preeclamptic placenta related to the TGF- $\beta$  pathway. *PLoS One* 10(10):e0141294.

(Sara Mishamandani is a research and communication specialist and Carol Kelly is a science writer for MDB Inc., a contractor for the NIEHS Division of Extramural Research and Training.)

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## Test kits can motivate parents to reduce allergens

*By Robin Mackar*

In-home test kits, coupled with patient education, help parents reduce allergen levels in their homes, according to NIEHS scientists. The researchers found that parents may become more motivated to participate in allergen reduction interventions when they can actually see results for themselves.

### Reducing dust mites

A research collaboration that included Darryl Zeldin, M.D., and Paivi Salo, Ph.D., from the NIEHS [Environmental Cardiopulmonary Disease Group](#), and others, specifically looked at dust mites.

Dust mites are microscopic relatives of the spider that live in dust on mattresses, bedding, upholstered furniture, carpets, curtains, and other soft furnishings. Dust mites contain allergens known to trigger symptoms in people who are allergic to them, and especially those with asthma.

“This is the first study to demonstrate that the use of an in-home test kit can lead to a reduction in dust mite allergen levels in the home,” said Zeldin, who is also the NIEHS scientific director. “It’s important to know what motivates people to adapt certain behaviors or attitudes, so we can develop more effective asthma prevention strategies.”

## Test kits monitor allergens

Sixty households in North Carolina, who had children aged 5-15 with dust-mite allergies, were enrolled in the study. Visits were made to all homes at the beginning, middle, and end of the study, to collect dust samples and have parents respond to questionnaires about their dust mite reduction behaviors. Samples were collected from the children's bedroom floors and beds, and the living room floors.

Half of the households received commercially available test kits at set intervals of one, two, five, and eight months, along with educational materials about reducing dust mites. The other half received only educational brochures about reducing dust mites at the same set intervals. The study lasted 12 months.

Households who received the test kits had a consistent reduction in dust mite allergens over the course of the study. There was a three-fold increase in the number of test kits showing undetectable levels of dust mite allergens over the study period.

Of the participants using the kits, 68 percent were surprised by how high their dust mite exposure was when first tested. These individuals also tended to strongly agree that the test kit results motivated them to adopt behaviors that led to a greater reduction in dust mites. For example, 63 percent of test kit participants reported using special allergen-proof pillow covers by the end of the study, compared to only 33 percent in the educational materials only group. Other changed behaviors included using allergen-proof mattress covers, washing sheets weekly in hot water, vacuuming with HEPA filters, and removing stuffed animals.

“Parents of asthmatic children have an extra long list of things to do to keep their kids healthy,” said Salo. “We wanted to see if having an easy-to-use kit, where parents could actually monitor allergen levels, would help parents start and maintain allergen reduction strategies, and our results suggest that it actually did.”

*Citation:* Winn AK, Salo PM, Klein C, Sever ML, Harris SF, Johndrow D, Crockett PW, Cohn RD, Zeldin DC. 2015. Efficacy of an in-home test kit in reducing dust mite allergen levels: results of a randomized controlled pilot study. *J Asthma*; doi:10.3109/02770903.2015.1072721 [Online 26 August 2015].

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*Zeldin's group conducts basic, clinical, and translational research to better understand the role of the environment in the development of respiratory and cardiovascular diseases, such as allergy, asthma, adult respiratory distress syndrome, atherosclerosis, hypertension, and stroke. (Photo courtesy of Steve McCaw)*



*Salo is an epidemiologist in the NIEHS Environmental Cardiopulmonary Disease Group. (Photo courtesy of Steve McCaw)*

# Variability among individuals spurs decision makers

By John Yewell

How individuals react to toxins, and how this influences the regulation of environmental pollutants, were the topics of an NIEHS-sponsored workshop in Washington, D.C. on Sept. 30 and Oct. 1.

“Interindividual Variability: New Ways to Study and Implications for Decision Making” was hosted by the [Committee on the Use of Emerging Science for Environmental Health Decisions](#) (see sidebar).

## Changes in our understanding of risk

Workshop chair Lauren Zeise, Ph.D., acting director of the Office of the Environmental Health Hazard Assessment of the [California Environmental Protection Agency](#), summarized the factors decision makers consider when writing regulations, and the role of scientists in helping them.

“Risk is balanced by technical feasibility, cost assessment, and a variety of other things,” she said. “If you really understand the risk and the benefit of different options, you have a much firmer ground for making decisions.”

NIEHS and National Toxicology Program (NTP) Director Linda Birnbaum, Ph.D., shed light on changes in our understanding of the complex interplay between genetics and environmental stressors. That interplay is key to the variable response that different individuals show to stressors or exposures, also known as interindividual variability.

“The tobacco companies blocked regulation of cigarette smoking for 50 or 60 years by pointing out that only 11 percent of people who smoke get lung cancer,” Birnbaum said. We now understand that susceptibility among people varies for genetic and environmental reasons, she explained. “We have to think about things like our diet, socioeconomic status, the totality of exposures, and stress, which can result in biochemical changes.”



*“Risk assessment is balanced by technical feasibility, cost assessment, and a variety of other things, to come up with a management option,” said Zeise. (Photo courtesy of the National Academies)*



*DeVito characterized his use of the diversity outbred (DO) mouse strain. “We may be missing things using a single strain of mouse,” he said. “The DO strain will help us characterize suspected toxicities we’re seeing in human populations that we did not pick up in traditional rodent studies.” (Photo courtesy of the National Academies)*

 **Linked video:** (Launches in new window)  
[Watch Birnbaum's opening presentation, "The Importance of Understanding Interindividual Variability in Response to Chemical Exposure," in this video from the workshop. \(33:02\)](#)  
Download Media Player:  Flash [↗](#)

## The four Ps

The revolution now underway in health care, known as [personalized medicine](#), strives to take that variability into account. “Health care today is expensive, reactive, inefficient, and focused largely on one-size-fits-all treatments for events of late stage disease,” said Jon Cook, Ph.D., senior director of investigative toxicology at Pfizer, Inc. “The answer is personalized, predictive, preventive, participatory medicine. The four Ps.”

Recalling Birnbaum’s figures on the percentage of people who may be naturally resistant to certain diseases, Cook explained that some patients get no benefit from drugs developed for wide use. “But they are still at risk for the drug’s side effects,” he said. “They have no benefit and all risk. As much as we think we know about science,” he added, “Mother Nature humbles us.”

## Science supporting regulation

Because of the approach to human health that is moving toward the individual, several speakers raised questions about the regulatory mechanisms designed to protect the broader population.

“In the arena of [Tox 21](#), for example,” said Michael DeVito, Ph.D., acting head of the NTP Laboratory at NIEHS, “we are talking about reinventing risk assessment. Fundamental shifts in the science underlie those decisions, but those decisions will always come back to the regulatory context.”



*Birnbaum encouraged taking a broad view of the environment. “I am defining environment in big terms, not only chemicals,” she said. (Photo courtesy of the National Academies)*



*“Diseases are complex. They are multifactorial,” said Cook. “The tools being developed by precision medicine will allow us to dissect disease into subclasses so we can target more effective treatments.” (Photo courtesy of the National Academies)*

John Vandenberg, Ph.D. and director of the Research Triangle Park Division of the [U.S. Environmental Protection Agency National Center for Environmental Assessment](#), used the example of ozone exposure to underscore the direction of targeted research. “About 15 percent are high responders, and about 15 percent have cast-iron lungs. Why are normals different? That is a key question that the research community has an opportunity to address.”

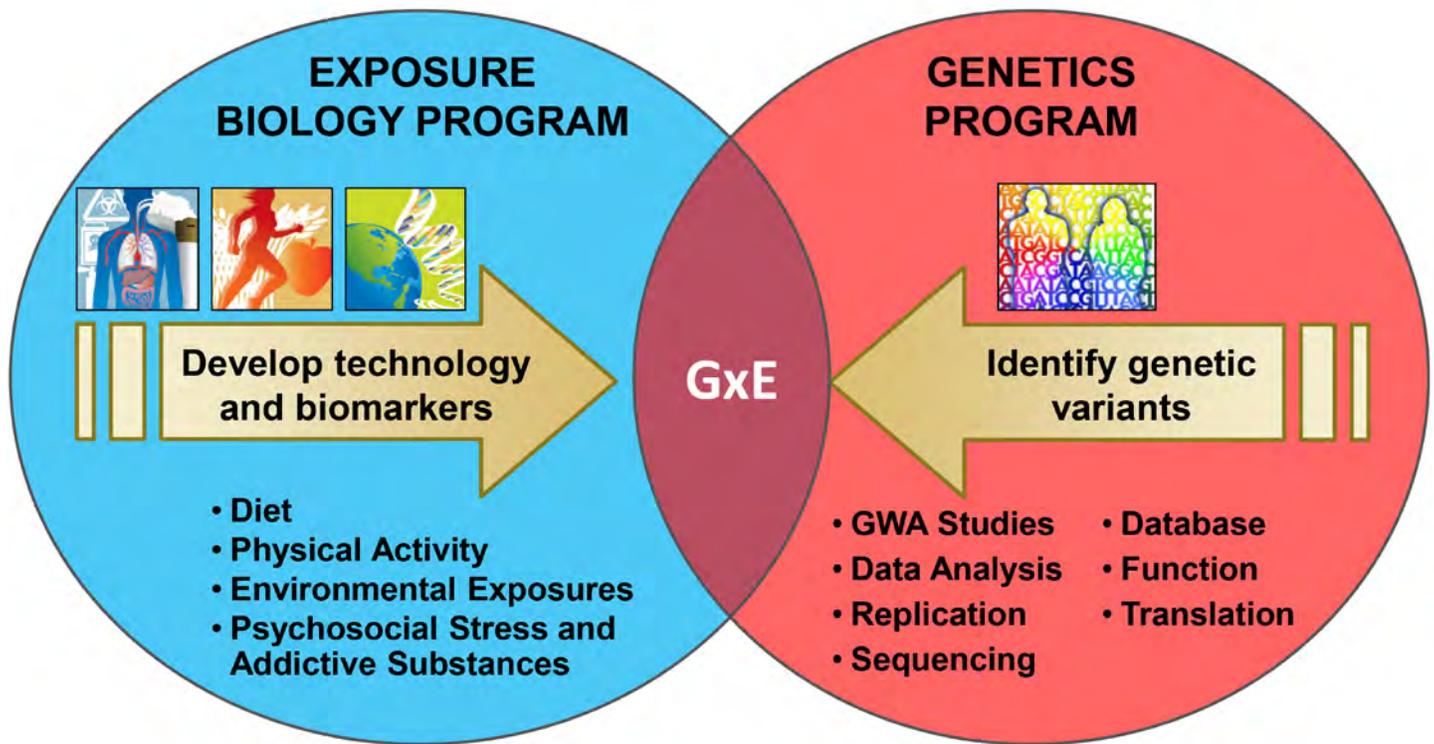
(John Yewell is a contract writer for the NIEHS Office of Communications and Public Liaison)

## Role of the NAS committee

The Committee on the Use of Emerging Science for Environmental Health Decisions was created by the National Academy of Sciences (NAS) in 2012, at the request of NIEHS.

The committee facilitates communication among government, industry, environmental groups, and the academic community on scientific advances related to environmental impacts on human health. Periodic workshops on topics of emerging interest help to clarify questions for scientific research.

# Genes, Environment and Health Initiative: The Vision



Birnbaum's presentation touched on the complex interactions between genetics and environmental exposure (GxE) in human health. GWA stands for genome-wide association. (Photo courtesy NIEHS)

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## Dolinoy receives NIH Transformative Research Award

By Virginia Guidry

NIEHS grantee Dana Dolinoy, Ph.D., has won a 2015 National Institutes of Health (NIH) Transformative Research Award. NIH Director Francis Collins, M.D., Ph.D., announced this and other awards from the [High-Risk, High-Reward Research](#) program on Oct. 6.

Although most NIH grants require demonstrated feasibility to be funded, the Transformative Research program invests in bold ideas that have not been tested because it would be cost-prohibitive to do so. Without preliminary data, applicants must emphasize innovation and scientific significance to be selected. Dolinoy was one of eight researchers to receive the award this year.

“This program has consistently produced research that revolutionized scientific fields by giving investigators the freedom to take risks and explore potentially groundbreaking concepts,” said Collins. “We look forward to the remarkable advances in biomedical research the 2015 awardees will make.”

## Building on innovation

Dolinoy is building on research launched by her 2009 NIEHS Outstanding New Environmental Scientist (ONES) award. The highly competitive ONES awards help promising early career scientists establish innovative environmental health research programs.

Dolinoy is an associate professor at the University of Michigan School of Public Health, leads its [Environmental Epigenetics and Nutrition Laboratory](#), and is a researcher with the university's NIEHS-U.S. Environmental Protection Agency [Children's Environmental Health and Disease Prevention Center](#). In addition, she is an associate director and research engagement program lead for the NIEHS-funded [Michigan Lifestage Environmental Exposures and Disease Center](#).

## Developing a new method of gene silencing

Dolinoy hopes to push the frontiers of epigenetic science with a four-year, \$2.4 million project called [Development of piRNAs for Target-Specific Methylation](#). There is growing evidence that environmental influences can affect the epigenome, or how genes are expressed, as well the genome or the genes themselves.



*“If successfully completed, this project will greatly transform the technologies currently used in epigenomics research and their translation to clinical settings,” said Dolinoy. (Photo courtesy of Dana Dolinoy)*

## High-Risk, High-Reward funding sparks innovations

Current NIEHS grantees who have received High-Risk, High-Reward program funding say that it has changed the direction of their careers.

**Donna Spiegelman, Sc.D.**, of the Harvard School of Public Health, received a 2014 Pioneer Award. She has expanded her research team to include five postdoctoral fellows who are focused on developing methods for integrating research findings into public health policy and practice, known as implementation science. Spiegelman's team is consulting with public health leaders from around the world about urgent methodological needs, such as identification of optimal, cost-effective cancer screening and implementation of environmental-level changes in the workplace to prevent diabetes and cardiovascular disease.

“The Pioneer Award funding has completely changed the makeup of my lab in exciting and sometimes unanticipated ways,” said **Oliver Rando, M.D., Ph.D.**, of the University of Massachusetts Medical School, who also received a 2014 Pioneer Award. “We have gone from being a yeast genomics lab to one heavily invested in mouse genetics, reproductive biology, and early development. It has been unspeakably exciting!”

**Manish Arora, Ph.D.**, of the Icahn School of Medicine at Mount Sinai, was granted a 2014 New Innovator Award. “The support from this grant allows me to study fetal programming by environmental stressors, and how this may impact long term health outcomes,” he said. “Some of the methods I use rely on sophisticated technology not traditionally used in environmental health, and this NIEHS mechanism makes it possible for me to access resources around the globe.”

Her team, including NIEHS grantee Christopher Faulk, Ph.D., from the University of Minnesota, and Maureen Sartor, Ph.D., from the University of Michigan, will use a class of ribonucleic acid (RNA) called Piwi-interacting RNA (piRNA) to develop technology that can detect and turn off genes that are likely to be defective. This process is called gene silencing.

This method of gene silencing produces permanent changes because it acts during transcription, the first step of gene expression when DNA strands are copied into RNA, rather than during translation, which is the final step that generates proteins.

Working with mice, the researchers will use visually evident outcomes, like changes in fur color or stress behaviors, to show that the method works. If successful, this groundbreaking approach will provide a way to alter the epigenome that is directly applicable to human disease.

(Virginia Guidry, Ph.D., is a technical writer and public information specialist in the NIEHS Office of Communications and Public Liaison.)

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## NIEHS shines at Environmental Mutagenesis and Genomics Society meeting

*By Deepa Singh*

NIEHS scientists and grantees met Sept. 26-30 at the 46th Environmental Mutagenesis and Genomics Society (EMGS) conference in New Orleans, Louisiana, and several received awards.

These annual meetings are known for bringing together leading scientists from academia, industry, and government to discuss developments in understanding environmental threats to genomic integrity, which can serve as groundwork for betterment of human health. The meeting featured a wide variety of topics, from DNA damage, DNA repair, and mutagenesis, to heritable effects and epigenetic alterations in genome function.

### Award lecture and keynote by NIEHS grantees

NIEHS grantee [Myron Goodman, Ph.D.](#), from the University of Southern California, received this year's EMGS Award for his contributions to the fields of DNA replication and mutation repair. His work has led to advancements in the areas of microbial evolution, cancer therapy, and immune response.

His talk, titled "Better Living with Hyper-Mutation," shed light on ways the improper regulation of hypermutations, which can be beneficial when tightly regulated, can give rise to haphazard clusters of mutations, which may result in cancer. Hypermutation is a process that helps the immune system respond to new foreign elements.



*Goodman presented the 2016 EMGS Award lecture. (Photo courtesy of Riverview Photography).*

NIEHS grantee, [Leona Samson, Ph.D.](#), gave a keynote presentation. Samson, a recipient of the National Institutes of Health (NIH) [Pioneer Award](#) and a professor at the Massachusetts Institute of Technology, studies the effects of alkylating agents on organisms ranging from bacteria to humans. These alkylating agents are toxic, mutagenic, and carcinogenic and have been used in treating cancer.

“Both Goodman and Samson shared their amazing science and interspersed their lectures with their unique perspectives on what it means to be a scientist,” said Sara Andres, Ph.D., a visiting fellow in the [Genome Stability Structural Biology Group](#), led by Scott Williams, Ph.D.

### **New researchers interact with seasoned scientists**

Michelle Heacock, Ph.D., a health science administrator in the NIEHS [Health Substances Research Branch](#), pointed out that NIEHS scientists from across the institute presented work during the event. “The meeting provided an opportunity to showcase the basic science conducted at NIEHS, as well as applied fields related to population health and regulatory science,” she said.

The meeting also served as a platform for early career researchers to share their work and interact with seasoned scientists.

“EMGS makes it a point to support new investigators by providing great networking opportunities and a platform to showcase their work,” Andres noted.

### **Exciting science by early career researchers**

Emphasizing the strong mentoring history of EMGS, Heacock said, “Some of the platform sessions and special interest group meetings feature talks given by postdocs, graduate students, and new investigators.”

Andres received the Best Talk by a New Investigator award for her presentation, “Ctp1 Orchestrates DNA Binding and Bridging in DNA Repair.” She said she hopes that the connections she has made will be helpful during her search for a position as an independent researcher.

Natalie Gassman, Ph.D., and Bret Freudenthal, Ph.D., former postdocs in the [DNA Repair and Nucleic Acid Enzymology Group](#), discussed the exciting research they are doing in their new positions. Both received NIH Pathway to Independence awards (see [story](#)).

Gassman described her work on how bisphenol A affects cell survival after oxidative stress. Freudenthal spoke on the genetic and biochemical studies that provide a basis for the mutagenic properties of 5-chlorocytosine, a known inflammation biomarker. He described findings that could suggest a functional link between chronic inflammation and cancer.

(Deepa Singh, Ph.D., is a visiting fellow in the NIEHS Mechanisms of Mutation Group.)

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*Heacock, who previously researched causes of cellular toxicity caused by DNA damaging agents, now supports the NIEHS Superfund Research Program. (Photo courtesy of Steve McCaw)*



*From left, Freudenthal, an assistant professor at the University of Kansas Medical Center; Gassman, an assistant professor at the University of South Alabama Mitchell Cancer Institute, Goodman, and Andres shared a light moment at the awards banquet. (Photo courtesy of Riverview Photography).*

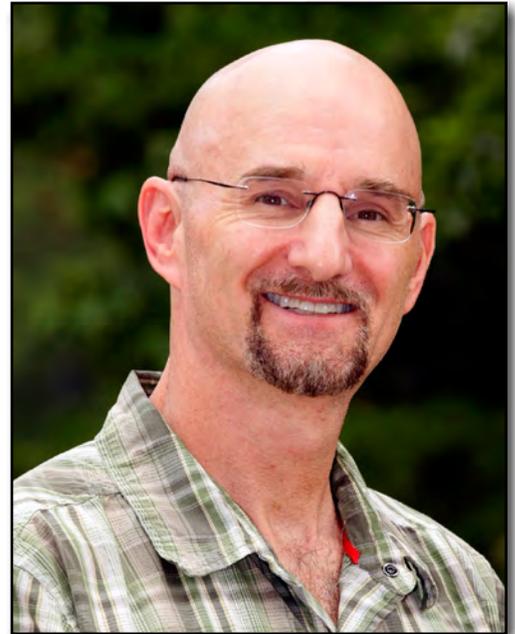
# Lab retreat links NIEHS researchers, alumni, and collaborators

By Geoffrey Feld

The NIEHS Genome Integrity and Structural Biology Laboratory (GISBL) celebrated its inaugural retreat Oct. 6-7 at the North Carolina Museum of Art in Raleigh, North Carolina. The event brought together NIEHS scientists past and present, as well as external collaborators and mentors, to share research and experiences.

“This is the first retreat of the combined program, merging the Laboratory of Molecular Genetics and most of the Laboratory of Structural Biology,” said laboratory head William Copeland, Ph.D., as he convened the meeting. “What we envisioned was a synergistic interaction between these two laboratories, and I think that’s what we’re having,” he added.

The retreat featured lectures from invited professors, as well as shorter talks and posters by trainees and staff. In a tradition dating to the 2012 retreat of the Laboratory of Structural Biology, poster presenters participated in Poster Flash, a series of two-minute introductions delivered to the group. The format inspired innovation, as biologist Scott Gabel, of the Nuclear Magnetic Resonance Group, summarized his data on the DNA repair protein XRCC1 in campaign promise fashion, to rousing applause.



*In addition to his work as head of the lab, Copeland leads the Mitochondrial DNA Replication Group. (Photo courtesy of Steve McCaw)*

## Staying connected

Highlighting personal connections among researchers provided one of the retreat’s themes. Postbaccalaureate fellow Chris Crowl, from the Environmental Genomics Group, introduced the first invited speaker — his undergraduate mentor, [Terry Furey, Ph.D.](#), from the University of North Carolina at Chapel Hill (UNC). Furey reported on an ongoing NIEHS-funded collaborative project that studies the effects of exposure to 1,3-butadiene, a plastic processing byproduct, in mice.

Current trainees attended a special session with trainee alumni of GISBL and its predecessors. The alumni had diverse scientific careers in academics, program management, project management, and medical writing. After describing their duties and the skills necessary to obtain and excel at their jobs, the alumni joined in a panel discussion to answer questions from the lab’s current trainees.

## Former trainee career panel

Current NIEHS grantees who have received High-Risk, High-Reward program funding say that it has changed the direction of their careers.

**Michelle Heacock, Ph.D.**, is a health scientist administrator with the NIEHS Superfund Research Program. She was formerly with the DNA Repair and Nucleic Acid Enzymology Group.

**Jordan St Charles, Ph.D.**, is a project manager with LabCorp Clinical Trials in Durham, North Carolina. She was formerly with the DNA Replication Fidelity Group.

**Yuan Liu, Ph.D.**, is an assistant professor with Florida International University in Miami. She was formerly with the DNA Repair and Nucleic Acid Enzymology Group.

**Jeff Stumpf, Ph.D.**, is an associate scientific director with MedThink Communications in Raleigh, North Carolina. He was formerly with the Mitochondrial DNA Replication Group.

## Repairing and organizing DNA

The Nobel Prize in Chemistry (see related [story](#)), announced on the second day of the retreat, was awarded for contributions to a topic at the center of the lab's research, DNA repair.

In his lecture on the DNA repair protein TREX1, [Fred Perrino, Ph.D.](#), of the Wake Forest School of Medicine, told of a competition that turned into a collaboration with new Nobel Laureate Tomas Lindahl, Ph.D. "There couldn't be a better person to win the Nobel Prize," Perrino said.

Although many of the talks on genome integrity focused on mutations of single or a few DNA base pairs, guest speaker [Kerry Bloom, Ph.D.](#), of UNC, presented what he called the 10,000-foot view of chromosomes, which are the complex organizational units of DNA. Using computational methods based solely on thermodynamic principles, combined with fluorescent imaging of live yeast cells, Bloom's lab developed a testable model of a chromosome that may explain why its structure is largely retained from yeast to humans.

The responsibility of planning, coordinating, and executing the retreat was carried out by GISBL Trainee Action Committee (TAC) volunteers. For their hard work, committee advisor and senior scientist Michael Resnick, Ph.D., honored the retreat planning committee with the Noble Effort Prize, a nod to the Nobel Prize announcement. "I feel very fortunate to be able to work with that group," he said.



*Invited speaker [Peter McKinnon, Ph.D.](#), from St. Jude Children's Research Hospital, discussed how mutations and deletions of DNA repair enzymes result in tumors and cancer in mice. He further reflected on the connection of his research with pediatric clinical data collected at St. Jude. (Photo courtesy of Steve McCaw)*



*Perrino's talk, "The TREX1 Pathway in Autoimmune Disease," featured studies of the TREX1 enzyme by retreat chair [Clinton Orebaugh, Ph.D.](#), who completed his graduate work in Perrino's lab and introduced the speaker. Building on Orebaugh's results, recent research in Perrino's lab further explains how mutations in TREX1 contribute to the human autoimmune diseases lupus and Aicardi-Goutieres syndrome. (Photo courtesy of Clinton Orebaugh)*



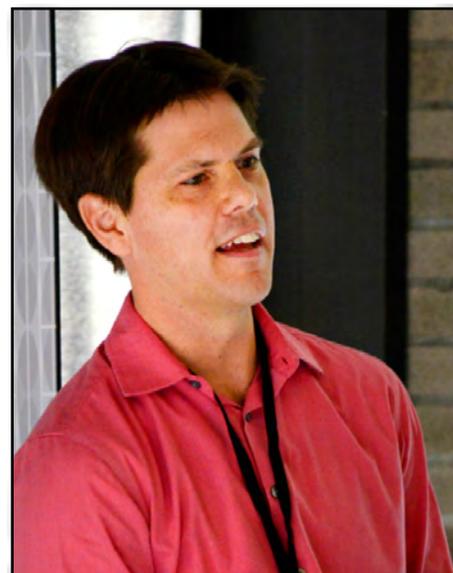
*While a student at UNC, [Crowl](#), right, had [Furey](#) as a professor and interned in [Bloom's](#) lab. [St Charles](#), left, applies her skills in organization and communication to ensure productivity of clinical labs as a LabCorp project manager. (Photo courtesy of Steve McCaw)*



*Liu says the driving force to pursue an academic career was her passion for researching across a lifetime. Her lab at Florida International University studies base excision repair, which is the major pathway cells use to combat oxidative DNA damage. Lindahl shared the 2015 Nobel Prize in Chemistry for pioneering the discovery of this pathway. (Photo courtesy of Steve McCaw)*



*While wrapping up her postdoc at NIEHS, Heacock took what she called a leap of faith, accepting an assignment to the NIEHS Division of Extramural Research and Training to gain science administration experience. (Photo courtesy of Steve McCaw)*



*As a medical writer at MedThink Communications, Stumpf coordinates with medical professionals and pharmaceutical companies to tell the scientific story of a new drug or therapeutic process. He said he enjoys tackling a diverse set of problems for clients while working as a member of a team. (Photo courtesy of Steve McCaw)*



*The GISBL retreat committee and TAC members played a pivotal role in the success of the event. From top left, Mark Itsko, Ph.D.; Orebaugh; Resnick; Karen Debalsi, Ph.D.; Melike Caglayan, Ph.D.; Crowl; Peter Thompson, Ph.D.; Molly Cook; Sara Andres, Ph.D.; Natalie Saini, Ph.D.; and Thuy-Ai Nguyen, Ph.D. Not pictured: Kelly Daughtry, Ph.D. (Photo courtesy of Steve McCaw)*



*The North Carolina Museum of Art offered attendees a scenic backdrop, complete with exhibits and walking trails to explore between sessions. “[It’s] the best place I’ve ever been for a retreat,” said Resnick. (Photo courtesy of Steve McCaw)*

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

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## This month in EHP

The November issue of Environmental Health Perspectives (EHP) takes a closer look at mortality related to extreme weather events, and hospital use of genome sequencing to study outbreaks of disease.

### Between Extremes: Health Effects of Heat and Cold

Although heat waves and cold snaps pose major health risks and grab headlines when they occur, recent studies have uncovered a more complex, and perhaps unexpected, relationship between temperature and public health.

### Outbreak Breakthrough: Using Whole-Genome Sequencing to Control Hospital Infection

As the cost and time required to sequence genomes has plummeted, hospitals around the world have been experimenting with whole-genome sequencing to study disease outbreaks occurring in their wards and special care units.

### Research summaries featured this month include:

- **Time and Temperature: Changes in Heat-Related Mortality Over 27 Years** — A new study indicates that the relative risk of heat-related mortality declined significantly over a 27-year period in the United States, Japan, and Spain, but found no evidence of a decline in the United Kingdom. This may mean that existing climate impact predictions for heat-related mortality may need to be revised.
- **Bias in Environmental Cohort Studies: The Example of Bone Lead and Mortality** — Unrecognized biases in prospective cohort studies may underestimate health consequences of environmental exposures. Researchers, using data from the Normative Aging Study, analyzed lead exposure in men and death from ischemic heart disease. They employed a diagramming method, directed acyclic graphs, to illustrate relationships between variables that could bias study results.

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<http://twitter.com/ehponline>



## Extramural papers of the month

By *Nancy Lamontagne*

- Exposure to phenols affects pubertal development in girls
- Recombinase enzymes recognize matching DNA three bases at a time
- Time between births associated with autism risk
- Faster measurements of brominated flame retardants

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

### Exposure to phenols affects pubertal development in girls

A new study finds that exposure to phenols, including some that are known to be endocrine disruptors, can affect the timing of puberty in girls. Early sexual maturation is associated with increased risk of breast cancer.

Although phenols are known to affect hormone activity, their effects on child reproductive development are not well studied. In the new study, researchers examined pubertal development among 1,239 girls who were enrolled in the Breast Cancer and the Environment Research Program Puberty Study when they were 6-8 years old. The girls, from three areas of the U.S., were followed annually for seven years to determine the age of first breast or pubic hair development. The researchers measured ten phenols in urine collected at enrollment.

The analysis revealed that girls with the highest levels of enterolactone and benzophenone-3 experienced breast development five to six months later compared to those with the lowest levels, with adjusted hazard ratios of 0.79 (0.64-0.98) and 0.80 (0.65-0.98), respectively. Breast development four to nine months earlier was observed for girls with the highest levels of triclosan and 2,5-dichlorophenol, with adjusted hazard ratios of 1.17 (0.96-1.43) and 1.37 (1.09-1.72), respectively.

The researchers suggested that benzophenone-3 and enterolactone may block production of the hormone androgen, and that triclosan and 2,5-dichlorophenol could affect thyroid hormones. Additional research is needed to confirm these findings and to identify any windows of susceptibility during which exposure might affect pubertal development.

*Citation:* Wolff MS, Teitelbaum SL, McGovern K, Pinney SM, Windham GC, Galvez M, Pajak A, Rybak M, Calafat AM, Kushi LH, Biro FM, Breast Cancer and Environment Research Program. 2015. Environmental phenols and pubertal development in girls. *Environ Int* 84:174-180.

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### Recombinase enzymes recognize matching DNA three bases at a time

The exchange of genetic information between DNA strands, known as DNA recombination, is important for DNA repair and also drives evolution. New research, funded in part by NIEHS, has revealed the physical basis for these DNA strand exchange reactions.

The study authors previously developed single-molecule methods to visualize DNA recombination, using an imaging technique known as total internal reflection fluorescence microscopy. Using this imaging approach and molecular dynamics simulation, they showed that members of the Rad51/RecA family of recombinase enzymes, which are responsible for DNA recombination, search for and recognize matching DNA strands three bases at a time.

The researchers studied four different recombinases — human Rad51, *Escherichia coli* RecA, eukaryotic forms of RecA, and *Saccharomyces cerevisiae* Dmc1. The imaging studies showed that bacterial RecA, the Rad51, and Dmc1 all stabilize intermediaries in the strand exchange in precise three nucleotide steps. They confirmed the finding using molecular dynamics simulation. Additionally, the researchers found that while Rad51, RecA, and Dmc1 can all step over DNA mismatches, only Dmc1, which is specialized for recombination during meiosis, can stabilize a mismatching triplet. This discovery provides insight into why eukaryotes evolved a recombinase that is specialized for meiosis.

*Citation:* Lee JY, Terakawa T, Qi Z, Steinfeld JB, Redding S, Kwon Y, Gaines WA, Zhao W, Sung P, Greene EC. 2015. Base triplet stepping by the Rad51/RecA family of recombinases. *Science* 349(6251):977-981.

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## Time between births associated with autism risk

A new study, funded in part by NIEHS, found that second-born children, conceived either less than two years or more than six years after the arrival of their older sibling, have an increased risk of autism spectrum disorders. Unlike other studies, the new study ruled out other autism risk factors that might account for the findings.

Previous studies have linked both short and long pregnancy intervals with increased autism risk. To further investigate the link between interpregnancy length and autism, the researchers designed a study that controlled for some potentially confounding factors. Data for the study came from the electronic medical records of about 45,000 children born between 2000 and 2009 in Kaiser Permanente's Northern California hospitals.

Autism was diagnosed in 0.81 percent of second-born children born three to four years after their older sibling. For second-born children with interpregnancy intervals of less than six months, autism prevalence was 2.11 percent; for intervals of six to eight months, 1.74 percent; and for intervals of six years or more, 1.84 percent. The results could not be explained by maternal body mass index (BMI), change in BMI between pregnancies, parental age, maternal antidepressant medication use, or unfavorable events occurring during the first or second pregnancy.

The researchers said that future studies that incorporate maternal nutritional status, especially folate and iron, and other factors, such as infertility, are necessary to understand the mechanisms involved in the association between autism and interpregnancy intervals.

*Citation:* Zerbo O, Yoshida C, Gunderson EP, Dorward K, Croen LA. 2015. Interpregnancy interval and risk of autism spectrum disorders. *Pediatrics* 136(4):651-657.

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## Faster measurements of brominated flame retardants

NIEHS grantees have developed a new method that can measure polybrominated diphenyl ether (PBDE) flame retardants and their analogs in human samples with a single 25-minute mass spectrometry analysis. The one-shot analysis technique would be cost-effective for large-scale studies examining the adverse health effects and accumulation patterns of brominated flame retardants.

PBDE flame retardants are commonly found in the environment and also accumulate in the human body. The hydroxylated (OH-BDE) and methoxylated (MeO-BDE) analogs of PBDEs are also of concern, because they accumulate in wildlife and humans. These forms naturally occur in the environment and can also result from biological transformation of manmade PBDEs. Typically, testing for flame retardants in human samples requires conversion of OH-BDEs into the more easily detectable MeO-BDEs. However, each compound must be measured separately, resulting in a series of time-consuming, expensive tests. To solve this problem, the researchers converted OH-BDEs into a similar, but alternate, compound allowing 12 PBDEs, 12 OH-BDEs, and 13 MeO-BDEs to be analyzed at once using gas chromatography with tandem mass spectrometry.

The researchers tested the method by measuring PBDEs and their analogs in paired human breast milk and serum samples from four people. Although the sample number was limited, the results showed different distribution profiles in serum and breast milk. The average concentrations of total PBDEs, OH-BDEs, and MeO-BDEs in breast milk were 59, 2.2, and 0.57 nanograms per gram of lipid, respectively. For serum, average concentrations were 79, 38, and 0.96 nanograms per gram of lipid, respectively.

*Citation:* [Butryn DM](#), [Gross MS](#), [Chi LH](#), [Schecter A](#), [Olson JR](#), [Aga DS](#). 2015. “One-shot” analysis of polybrominated diphenyl ethers and their hydroxylated and methoxylated analogs in human breast milk and serum using gas chromatography-tandem mass spectrometry. *Anal Chim Acta* 892:140-147.

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

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## Intramural papers of the month

*By Robert Brown, Greg Buchold, Deacquita Diggs, Gabriel Knudsen, and Qing Xu*

- [NTP finds molecular differences between hepatoblastomas and hepatocellular carcinomas](#)
- [Mitochondrial POLG2 disease variants impair cellular energy production](#)
- [Transient metal ions mediate the direction of DNA synthesis](#)
- [The AF-2 domain of estrogen receptor alpha suppresses AF1](#)
- [Improved detection methods for environmental chemicals](#)

# NTP finds molecular differences between hepatoblastomas and hepatocellular carcinomas

National Toxicology Program (NTP) researchers demonstrated that mouse hepatoblastomas (HB) are molecularly distinct from hepatocellular carcinomas (HCC). They also determined that, at the genomic level, mouse HB is similar to human HB. The work suggests that mouse HB is a suitable model for evaluating human cancer.

HB, a poorly differentiated embryonal neoplasm that typically occurs late in life in the mouse, is commonly associated with HCC. Historically, scientists believed HB was a malignant variant of hepatocellular tumors despite morphological differences. To address the question of origin and whether mouse HB is relevant to human HB development following chemical exposures, HB, HCC, and normal liver samples from B6C3F1 mice were used to determine relationships in global gene expression and mutation spectra of *Ctnnb1* and *Hras*, two common hepatic cancer genes.

The researchers found mouse and human HB share similarities at the pathway level, including embryonic development pathway dysregulation, stem cell pluripotency pathways, and genomic imprinting. In contrast, HB and HCC had strikingly different global gene expression and mutation spectra, although both may arise from a common hepatic progenitor cell. The authors suggest that exome sequencing at high read depths and cell lineage tracing experiments may further define the cellular origin of HB. **(GK)**

*Citation:* [Bhusari S, Pandiri AR, Nagai H, Wang Y, Foley J, Hong HL, Ton TV, DeVito M, Shockley KR, Peddada SD, Gerrish KE, Malarkey DE, Hooth MJ, Sills RC, Hoenerhoff MJ. 2015. Genomic profiling reveals unique molecular alterations in hepatoblastomas and adjacent hepatocellular carcinomas in B6C3F1 mice. Toxicol Pathol; doi:10.1177/0192623315599853 \[Online 18 August 2015\].](#)

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# Mitochondrial POLG2 disease variants impair cellular energy production

According to NIEHS scientists, a disease variant of the human mitochondrial DNA (mtDNA) polymerase gamma p55 subunit, encoded by the POLG2 gene, is unable to properly bind to the p140 catalytic subunit encoded by POLG. As a result, the energy reserve in each cell is greatly diminished, and the patient develops POLG2-related disease. Understanding the mechanisms that lead to the development of mitochondrial disease will help scientists design therapies to treat these debilitating conditions.

The p55 homodimer binds to the catalytic subunit forming the polymerase gamma trimer. Polymerase gamma is responsible for replication and repair of mtDNA. Because all currently identified POLG2 patients harbor heterozygous mutations, and because monomers within the p55 homodimer do not readily dissociate, the authors theorized that patients harbor a mixture of p55 molecules: 25 percent wild-type homodimers, 25 percent variant homodimers, and 50 percent heterodimers.

Using a tandem affinity strategy to study p55 variant heterodimers, the researchers found that one variant was dominant negative when associated with wild type and disturbed the mtDNA replication machinery. When they tagged p55 disease variants with green fluorescent protein and transfected them into human cells, two additional disease variants were found to misfold and were unable to localize to mtDNA. Both phenomena led to decreased respiratory capacity. This study aids in our understanding of how these complex disorders develop and provides valuable cell line models of mitochondrial disease. **(RB)**

*Citation:* [Young MJ, Humble MM, DeBalsi KL, Sun KY, Copeland WC](#). 2015. POLG2 disease variants: analyses reveal a dominant negative heterodimer, altered mitochondrial localization and impaired respiratory capacity. *Hum Mol Genet* 24(18):5184-5197.

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## **Transient metal ions mediate the direction of DNA synthesis**

NIEHS researchers have revealed that transient metal ions are essential for DNA polymerase beta (pol beta) to carry out its reverse reaction, or pyrophosphorolysis. The findings help scientists understand the mechanisms of DNA replication and may aid in the development of pharmaceutical treatments for cancer.

Pol beta catalyzes DNA synthesis, which is its forward reaction, and pyrophosphorolysis. While the enzyme adds one nucleotide to the DNA primer during DNA synthesis, it excises the primer terminal nucleotide during pyrophosphorolysis, making the DNA one base shorter. Since the removal of chain-terminating nucleotides during HIV/AIDS therapy and cancer chemotherapy may cause drug resistance, understanding the events involved in this reaction with all DNA polymerases is vital to effective drug design.

Previous data had shown that DNA polymerases use two metal ions, known as catalytic and nucleotide-binding metals, for the DNA synthesis reaction. The NIEHS team, however, identified a new metal ion-binding site in the enzyme. In this study, the researchers modeled the role of metal ions in pyrophosphorolysis by using computational calculation and biochemical assays. They found that the new metal ion is required to initiate the reaction of pyrophosphorolysis, but must be removed later for the reaction to proceed. Similar to a game of tug of war, the transient metal ions contribute to shifting the reaction in the reverse. **(QX)**

*Citation:* [Perera L, Freudenthal BD, Beard WA, Shock DD, Pedersen LG, Wilson SH](#). 2015. Requirement for transient metal ions revealed through computational analysis for DNA polymerase going in reverse. *Proc Natl Acad Sci U S A* 112(38):E5228-E5236.

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## **The AF-2 domain of estrogen receptor alpha suppresses AF1**

The C terminus ligand binding domain (AF-2) of estrogen receptor alpha (ERalpha) can inhibit the ligand-independent activation function in the N terminus (AF-1) of ERalpha, according to a team led by NIEHS researchers. The finding explains how the binding of estrogen activates its receptor by disrupting the inhibitory AF-2/AF-1 interaction. Since many estrogen-dependent tumors are treated with selective estrogen receptor modulators (SERMs) that inhibit ERalpha activity, discovery of this mechanism may help to determine the exposure risk from SERMs and other xenoestrogens.

The scientists assigned various estrogenic compounds to distinct categories, using a cell culture-based assay with different mutant forms of ERalpha lacking the AF-1 domain, or mutations in single nucleotides of distinct structural regions within the AF-2 domain. They propose a model in which the inhibitory interaction of one subregion of AF-2 with AF-1 is suppressing other activating interactions, including another copy of the receptor which allows dimerization or interaction with activating cofactors (coregulator proteins). How estrogenic compounds produce distinct effects in different tissues is under study. **(GB)**

*Citation:* Arao Y, Coons LA, Zuercher WJ, Korach KS. 2015. Transactivation function-2 of estrogen receptor alpha contains transactivation function-1-regulating element. *J Biol Chem* 290(28):17611-17627.

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## Improved detection methods for environmental chemicals

Researchers at NIEHS recently proposed a novel covariate-adjusted standardization method that effectively stabilizes the variability in urinary measures by adjusting for diluteness using excreted creatinine. Measuring environmental chemicals in urine or blood can be error-prone, due to variations in urinary diluteness caused by recent water intake and in blood concentrations of lipophilic chemicals caused by recent fat consumption. A similar standardization method for blood measurements adjusts for serum lipid levels.

To measure chemicals in urine, seven approaches were compared by means of data simulated to mimic a variety of realistic causal scenarios. Of those approaches, the proposed new method, which divides by the ratio between the observed and the covariate-predicted creatinine level, performed best. Depending on the causal scenario judged to capture the research setting, one might simultaneously need to separately adjust for creatinine as a covariate in the model.

In scenarios where lipophilic chemicals are measured in serum, a separate set of simulations revealed that the method that calls for dividing by serum lipids out-performed an alternative method that has recently been promulgated as superior. Therefore, the more classical approach for lipid adjustment is evidently better suited for epidemiological studies. **(DD)**

*Citation:* O'Brien KM, Upson K, Cook NR, Weinberg CR. 2015. Environmental chemicals in urine and blood: Improving methods for creatinine and lipid adjustment. *Environ Health Perspect*; doi:10.1289/ehp.1509693 [Online 24 July 2015].

(Robert Brown, Ph.D., is an Intramural Research and Training Award (IRTA) fellow in the NIEHS Cell Biology Group. Greg Buchold, Ph.D., is a former NIEHS postdoctoral fellow in the NIEHS Reproductive and Developmental Biology Laboratory. Deacquita Diggs, Ph.D., is a National Health and Environmental Effects Laboratory fellow in the U.S. Environmental Protection Agency Developmental Toxicity Branch. Gabriel Knudsen, Ph.D., is a research fellow in the National Cancer Institute, Center for Cancer Research, Laboratory of Toxicology and Toxicokinetics. Qing Xu is a biologist in the NIEHS Metabolism, Genes, and Environment Group.)

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# Inside the Institute

## Schrader looks for bigger fish to fry in retirement

By Robin Arnette, Kelly Lenox, and Robin Mackar

NIEHS bade a fond farewell to Deputy Scientific Director Bill Schrader, Ph.D., upon his Sept. 30 retirement. After a career committed to science, including the past 12 years in the institute's Division of Intramural Research, Schrader is looking forward to his much-anticipated fishing time.

"Bill has done an outstanding job as deputy scientific director and as the NIEHS training director," said Darryl Zeldin, M.D., NIEHS scientific director. "We will miss him greatly."

Ken Korach, Ph.D., head of the NIEHS Reproductive and Developmental Biology Laboratory, emceed the Sept. 28 retirement festivities. "We all know how much Bill loves to prepare spreadsheets, so we want to present him with one that he will remember us by," said Korach, as he and Schrader unfurled a two-sided spreadsheet more than seven feet long. Korach also called five people up from the crowd to show how many it would take to do Schrader's job.

After his colleagues and friends finished sharing stories, jokes, and good wishes, Schrader threatened, with characteristic good humor, to not retire after all. "I am still smiling over some of the roasts that I received at the hands of my former friends," he ribbed.

NIEHS and National Toxicology Program Director Linda Birnbaum, Ph.D., also thanked Schrader for his contributions to the institute. "Hundreds of trainees have benefitted from his guidance and enthusiasm," she said. "And I could always count on him to step up to the microphone at seminars and meetings and ask that probing question." In turn, Schrader presented Birnbaum with a science-based bumper sticker for her energy-efficient car.

### Paul Wade steps in as acting deputy

With Schrader's departure, Zeldin announced that Paul Wade, Ph.D., deputy chief of the NIEHS Epigenetics and Stem Cell Biology Laboratory, will serve as the acting deputy scientific director.



*Schrader, a biochemist and molecular endocrinologist, served on the faculty and administration at Baylor College of Medicine, as vice president for endocrine research at Ligand Pharmaceuticals, and co-founded Xenopharm Inc., before coming to NIEHS in 2003. (Photo courtesy of Steve McCaw)*

## Other changes in NIEHS leadership

October saw another transition in NIEHS leadership, as Executive Officer and Associate Director for Management Joellen Austin moved to Bethesda, Maryland, to serve as the associate director for management at the National Institute on Drug Abuse.

"I am happy for Joellen and this next big adventure, but sad that she will be leaving us after just four years," said Birnbaum.

Chris Long, deputy executive officer, will serve as acting associate director for management.

Wade, who came to NIEHS in 2004, and received NIH tenure in 2009, leads the Eukaryotic Transcriptional Regulation Group, and serves as director of the NIEHS Epigenomics Core Facility. Prior to joining NIEHS, Wade trained at Indiana University and the National Institute of Child Health and Human Development, and he held a faculty position at Emory University.

“We’re fortunate to have someone of Paul’s caliber taking the reins,” Zeldin said.



An avid fisherman, Schrader was thrilled with the cake, which came complete with a lure and miniature boat and fisherman. (Photo courtesy of Steve McCaw)



First speaker Korach voiced the heart-felt thanks of everyone in the room. (Photo courtesy of Steve McCaw)



NIEHS Molecular Genomics Core Laboratory Acting Director Kevin Gerrish, Ph.D., left, and Wade enjoyed the festivities. Wade will fulfill Schrader’s duties as acting deputy scientific director, while continuing to pursue his research on chromatin architecture and its influence on gene expression. (Photo courtesy of Steve McCaw)



From left, Joel Abramowitz, Ph.D., special assistant to the NIEHS scientific director, and Birnbaum greeted Schrader’s daughter Meg O’Brien and wife Phyllis. Abramowitz and Schrader were longtime colleagues. (Photo courtesy of Steve McCaw)



*Zeldin and Birnbaum presented a certificate to Schrader for his exemplary service to NIEHS. (Photo courtesy of Steve McCaw)*



*John Cidlowski, Ph.D., head of the NIEHS Signal Transduction Laboratory, has known Schrader for many years and said that his old friend displayed superb leadership of in-house researchers during his tenure. (Photo courtesy of Steve McCaw)*



*In typical comedic fashion, Schrader wrapped himself up in the spreadsheet Korach gave him. (Photo courtesy of Steve McCaw)*



*As training director, Schrader collaborated closely with Tammy Collins, Ph.D., left front, director of the Office of Fellows' Career Development, and Samantha Hoopes, Ph.D., middle front, chair of the NIEHS Trainees Assembly steering committee. (Photo courtesy of Steve McCaw)*



*Trevor Archer, Ph.D., head of the NIEHS Epigenetics and Stem Cell Biology Laboratory, traveled down memory lane to the time when he attended an endocrine conference as a young postdoc and met Schrader, who was a professor at Baylor College of Medicine in Houston. (Photo courtesy of Steve McCaw)*



*Schrader showed off the box stuffed with crackers, from Kesia Register and the rest of the NIEHS cafeteria staff. It seems Schrader was known for never missing a chance to enjoy crackers. (Photo courtesy of Steve McCaw)*



*John Pritchard, Ph.D., was among the former colleagues who returned to help celebrate Schrader's retirement. Pritchard formerly served as NIEHS acting scientific director and head of the Laboratory of Pharmacology and Chemistry. (Photo courtesy of Steve McCaw)*



*NIEHS Administrative Specialist Barbara Dietz, at podium, organized the party, and presented Schrader with a memory book containing photos, mementoes, and good wishes from across the institute. (Photo courtesy of Steve McCaw)*

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**National Institute of  
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