

July 2015

NIEHS Spotlight



[Climate justice conference focuses on needs of vulnerable populations](#)

“Responding to Emerging Health Effects” drew scientists, public health professionals, and community members to the conference at NIEHS.



[Council digs into a day of data](#)

At the June 2 meeting of the advisory council, big data emerged as a theme among the many topics covered.



[Tox21 tools promoted at UC Davis meeting](#)

A delegation of scientists from NIEHS and NTP promoted high throughput screening tools at a meeting June 18-19 at the University of California, Davis.



[Scholars Connect kicks off fourth year of boot camp](#)

The NIEHS Scholars Connect Program welcomed five fresh recruits June 8 to a weeklong boot camp in laboratory techniques.



[NIEHS marks advances in diversifying the biomedical workforce](#)

NIEHS announced six awards in the Undergraduate Research Education Program (UP) to Enhance Diversity in the Environmental Health Sciences.

Clinical Feature



[NIEHS participates in first international myositis conference](#)

NIEHS researcher Lisa Rider, M.D., gave several presentations at the First International Conference on Myositis, in May.

Science Notebook



[NTP completes chemical spill studies, finds water advisory level protective](#)

NTP studies may reassure West Virginia residents impacted by a chemical spill that there is very little reason for concern about long-term health effects.



[Walker delivers one-two punch for chemotherapy and antibiotics](#)

Graham Walker, Ph.D., discussed translesion synthesis polymerases at a May 28 Keystone lecture, and implications for anticancer drugs and new antibiotics.



[Is cancer mainly bad luck? NIEHS scientists respond](#)

NIEHS scientists weigh in with a JNCI commentary on the paper published by the journal Science in January regarding the role of luck in cancer.



National Institute of
Environmental
Health Sciences

[Tell the Environmental Factor what you think](#)

Starting in June, some readers may complete a survey when visiting Environmental Factor pages. Please respond to help us better meet your needs.



[Ethics Day marks sixth year with presentation by Nobel laureate](#) 🏆

NIEHS continues its award-winning Ethics Day program with a standing-room-only talk by Nobel prize winner Oliver Smithies, D.Phil.



[Seven promising Superfund trainees receive K.C. Donnelly award](#) 🏆

The K.C. Donnelly Externship Award Supplement supports SRP trainees pursuing transdisciplinary and translational opportunities.



[Public forum highlights progress on replacing animals used in safety testing](#)

Federal agencies shared progress and answered questions on finding alternatives to using animals in product safety testing at the May 27 event.



[Innovative training program launched in the wake of Ebola](#)

The NIEHS Worker Training Program brought experts together to discuss training needs for future infectious disease outbreaks.



[New data tools top the agenda at NTP board meeting](#)

New and maturing tools to aid the systematic review process and overall NTP research efforts took center stage at the June 16 NTP Board of Scientific Counselors meeting.



[Metabolomics as a tool for exposure science](#) ▶ Audio

Experts from across the U.S. and Europe gathered to discuss the potential of metabolomics studies to shed light on exposures of human populations.



[NTP toxicologist Nigel Walker, Ph.D., earns prestigious award](#) 🏆

Walker's contributions were recognized with the Herbert E. Stokinger Award from the American Conference of Governmental Industrial Hygienists.



[Exposure to low levels of chemical mixtures linked with cancer](#)

An international group of cancer researchers found carcinogenic potential in low-dose exposures to mixtures of chemicals that might not be carcinogenic alone.



[This month in EHP](#)

The July issue of Environmental Health Perspectives (EHP) examines the difficulties in developing safer food package to reduce chemical leaching.

Inside the Institute



[Preparing for the unthinkable](#)

Four months in the planning, Operation Sleipnir tested NIEHS emergency response to an active shooter scenario.

Extramural Research

[Extramural papers of the month](#)

- [Monitoring gene mutation using low volume blood samples](#)
- [3-D cell culture provides model to study toxicant effects on endocervix](#)
- [Faster assessment of carcinogenic potential for PAH mixtures](#)
- [Th17 cells convert into regulatory T cells during immune response](#)

Intramural Research

[Intramural papers of the month](#)

- [NTP develops tool to analyze and characterize Tox21 data](#)
- [What's luck got to do with cancer?](#)
- [Calcium sensor protein necessary for the development of psoriasis](#)
- [Heart rate variability in relation to Parkinson disease risk](#)
- [Lack of cross-reactivity between GST allergens could lead to new diagnostic tools](#)

Calendar of Upcoming Events

- **July 8**, Keystone 1003AB, 10:30 – 11:30 a.m. — NIEHS Office of the Director Special Seminar featuring Qamar Rahman, Ph.D., D.Sc.(h.c.), speaking on “Women! A Vulnerable Population in Occupational Settings”
- **July 9 (webinar)**, 1:00 – 3:00 p.m. — NIEHS Superfund Research Program Progress in Research webinar, “Reducing Exposure to Mercury, Arsenic, and Asbestos,” presented with the U.S. Environmental Protection Agency, [register](#)
- **July 10 (webcast)**, 2:00 – 3:00 p.m. — NIEHS hosts “Virtual Forum on Near-Roadway Pollution and Health,” [register](#)
- **July 13-14**, Rodbell Auditorium, July 13, 8:30 a.m. – 5:30 p.m.; July 14, 8:30 a.m. – 4:00 p.m. — Workshop on “Statistical Approaches for Assessing Health Effects of Environmental Chemical Mixtures in Epidemiology Studies,” [register](#)
- **July 15 (Off-site event)**, National Institutes of Health (NIH) Natcher Conference Center in Bethesda, Maryland, 9:00 a.m. – 3:30 p.m. — NIH Graduate and Professional School Fair, [register](#)
- **July 20**, Rodbell Auditorium, 10:30 – 11:30 a.m. — NIEHS Office of the Director seminar, “Charting Our Future Together: Setting an Agenda for the National Heart, Lung, and Blood Institute,” by Gary Gibbons, M.D., director of NHLBI.
- **July 29 (Off-site event)**, NIH Masur Auditorium in Bethesda, Maryland, 11:30 a.m. – 1:00 p.m. — Rwandan Health Minister Agnes Binagwaho, M.D., Ph.D., presents [Barnes Global Health Lecture](#), “Medical Research and Capacity Building for Development: The Experience of Rwanda,” sponsored by the Fogarty International Center and the National Institute of Dental and Craniofacial Research, [webcast](#)
- **July 30**, Rodbell Auditorium, 9:00 a.m. – noon — Summer Internship Program Poster Session
- View More Events: [NIEHS Public Calendar](#)

NIEHS Spotlight

Climate justice conference focuses on needs of vulnerable populations

By John Yewell

More than 100 scientists, public health professionals, and community members from across the nation converged on the NIEHS campus June 8-9 for the 2015 Department of Health and Human Services (HHS) [Climate Justice Conference](#), “Responding to Emerging Health Effects.”

The event, organized by the [HHS Environmental Justice Working Group](#), attracted attendees from federal, state, and local agencies, as well as representatives of community nonprofit groups and unions, with 55 more participating via webcast.

Risks affect the most vulnerable

In a keynote address, Wanda Jones, Dr.P.H., Principal Deputy Assistant Secretary for Health at HHS, described the populations at greatest risk from the effects of climate change. “[They are] the most vulnerable among us,” she said, “children, the elderly, those living in poverty, those with underlying health conditions, people in certain geographic areas, and those already bearing a disproportionate burden of environmental exposures.”

Her comments echoed those of Gwen Collman, Ph.D., director of the NIEHS Division of Extramural Research and Training. She said the conference was a place to share information, to “reduce the health risks for the most vulnerable populations, both in the United States and around the world.”

According to Mustafa Ali, of the U.S. Environmental Protection Agency, the broad representation at the conference would help bring about the necessary holistic approach to addressing climate change impacts on communities. Ali leads the federal Interagency Working Group on environmental justice.

Community perspectives

Representatives of community organizations provided a grassroots perspective, beginning with [Jalonne White-Newsome, Ph.D.](#), director of federal policy for West Harlem Environmental Action (WE ACT) for Environmental Justice. “We need to try to integrate and use research to inform policy, and [to] educate those folks that have the purse strings in their hands, who can in turn help community folks to survive,” she said.



In her keynote address, Jones described the HHS Environmental Justice Working Group and its priorities. “HHS considers climate change to be one of the top public health challenges of our time,” she said. (Photo courtesy of Steve McCaw)



Sandra Howard is senior environmental health advisor in the HHS Office of the Assistant Secretary for Health and one of the key organizers of the conference. (Photo courtesy of Steve McCaw)

Arturo Archila, an activist educator and job placement specialist with [Make the Road New York](#), said the community he represents was disproportionately affected by Superstorm Sandy, and the recovery process offered important lessons. “What really impressed me post-Sandy was that the best solutions [to linking response teams and local communities] came from the community itself,” he said.

However, community groups face hurdles when participating in research and response efforts, according to Elizabeth Yeampierre, J.D., executive director of UPROSE in Brooklyn and a former member of the NIEHS National Environmental Health Sciences Advisory Council. “Funders don’t always understand the breadth and complexity of what it takes to engage the community,” she said.

Yeampierre underlined the value of communities such as the one she represents, when it comes to issues of sustainability. “If you come from struggle, you have lived sustainably,” said Yeampierre. “Repurpose, reuse, recycle — there’s nothing more sustainable than a poor person.”

Tools for leaders and community members alike

Epidemiologist George Luber, Ph.D., chief of the [Climate and Health program](#) at the Centers for Disease Control and Prevention, described the [National Environmental Public Health Tracking Network](#), to help leaders anticipate effects of climate change on local health.

Another a set of powerful tools for researchers and decision makers was available for conference participants to explore. Mark Shimamoto, of the U.S. Global Change Research Program, demonstrated the [Climate Resilience Toolkit](#), which was promoted in March as part of the President’s Climate Data Initiative (see [story](#)). Shimamoto also led participants through the [climate portion of the Data.gov website](#), which provides hundreds of databases for analyzing climate trends and effects.

As the workshop drew to a close, Joseph (Chip) Hughes, director of the NIEHS Worker Training Program and one of the key organizers of the conference, reflected on what was achieved. “This event went way beyond my dreams,” he said “in terms of creating a community of practice around this issue.”

A report will be posted on the conference website.



“Climate change is global, climate impacts are local,” said John Balbus, M.D., NIEHS senior advisor for public health, who delivered a keynote address. (Photo courtesy of Steve McCaw)



“We need to make sure that [evaluations] happen,” said White-Newsome. “We have to make sure that the guidance and tools that are being developed [to integrate environmental justice concerns into government actions] are used.” (Photo courtesy of Steve McCaw)



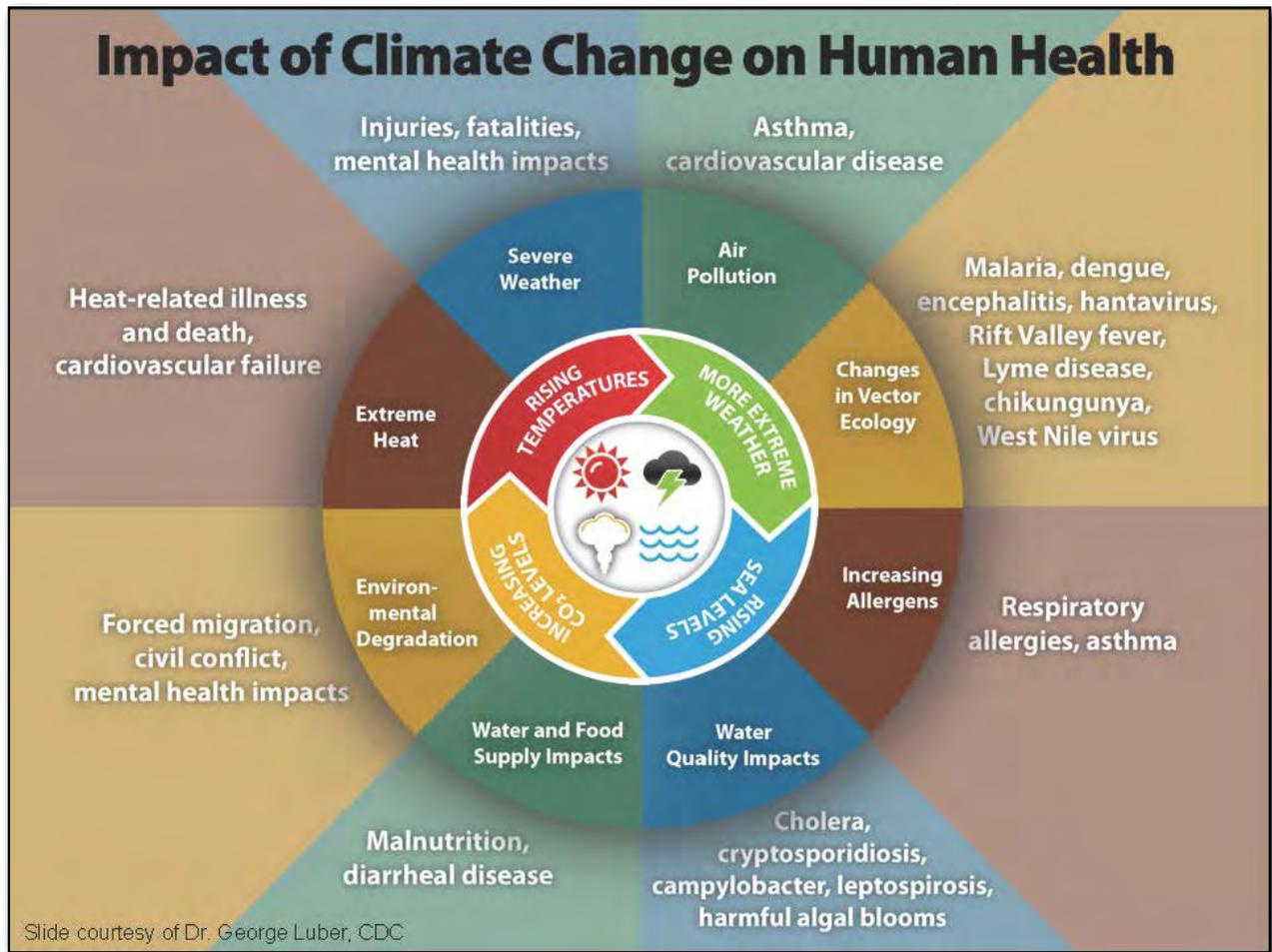
Sacoby Wilson, Ph.D., from the Maryland Institute for Applied Environmental Health gave a wide-ranging talk, touching on issues such as food access and the sovereignty of tribal communities. (Photo courtesy of Steve McCaw)



As we're talking about funding, as we're talking about research, we cannot forget our humanity," Archila said. (Photo courtesy of Steve McCaw)



The conference format included breakout sessions, such as the one above, during which participants dug deeper into issues of policy development and dissemination; education and training; research and data collection, analysis, and utilization; and services. (Photo courtesy of Steve McCaw)



Balbus shared a [graphic](#) from Luber detailing the drivers of climate change, center; the environmental consequences, middle ring; and associated human health effects, outside. (Photo courtesy of CDC)

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

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Council digs into a day of data

By Ernie Hood

At the June 2 [145th session](#) of the National Advisory Environmental Health Sciences Council, big data emerged as a theme among the many topics covered during the day. Collaborations, big data, data sharing, and data science are increasingly important considerations for the entire scientific community. And when it comes to data, the field of environmental health sciences faces its own challenges and opportunities.

Starting the conversation

NIEHS used the session to mine the experience and wisdom of council members on how to move forward in data science and serve the needs of researchers. “We are enablers of research here at NIEHS, so we want to understand how these issues impact the way all of you do your work,” said session moderator Cindy Lawler, Ph.D., from the Division of Extramural Research and Training (DERT). Council members responded with a robust discussion of their data needs and suggested future directions.

Lawler broadly defined data science as being concerned with the so-called four Vs — volume, velocity, variety, and veracity. Marie Lynn Miranda, Ph.D., from the University of Michigan, homed in on the third. “I would make the case that NIEHS has a comparative advantage in approaching and focusing on the variety,” she observed. “And in order to do that, there needs to be a little bit of culture change at the institute and amongst the broad community of people associated with it.”

Specifically, Miranda advocated for increased support of training in data sciences and enhanced efforts to make NIEHS programs more conducive to the involvement of statisticians and informaticians in research.

Council member Andrew Feinberg, M.D., from the Johns Hopkins School of Medicine, emphasized the need for standardization. “The environmental health issue is [that] we need to define rigorous standards for the sorts of data that will be collected,” he said. By falling into certain acceptable ranges, he added, such data will be more useful and translatable across other studies.



“Data science is one of the cross-cutting themes in our strategic plan,” said Lawler, who leads a workgroup focused on coordinating data science across the NIEHS grant programs. (Photo courtesy of Steve McCaw)



Miranda, right, and Feinberg, both made valuable contributions to the data science discussion. (Photo courtesy of Steve McCaw)

Other data matters

DERT Director Gwen Collman, Ph.D., also discussed data science in her division update, with a focus on data sharing and the institute's substantial investments in environmental epidemiology. She announced the launch of the [Epidemiology Resources Catalog](#), a new online resource for researchers and the public that provides information about DERT cohort, case-control, and cross-sectional studies.

“Our goal is to facilitate new collaborations, or support existing collaborations, maximizing our investments in these areas,” she said. The first of three planned phases — a searchable table — is now online, to be followed by individual detailed pages for each listed grant, and improved search and filter functions.

Philip Bourne, Ph.D., associate director for data science at the National Institutes of Health (NIH), participated remotely, giving a talk titled “NIH as a Digital Experience.” He defined the data science goals of NIH, and discussed the five action areas in the NIH data science strategy — sustainability, workforce development and diversity, discovery and innovation, policy and process, and leadership. The mission is, he said, “to foster a sustainable, efficient, and productive data science ecosystem.”

Beyond the data

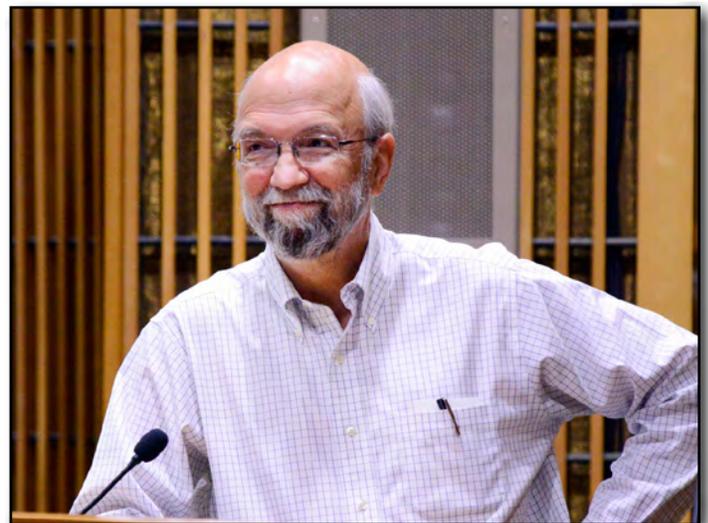
Although data dominated the day, the councilors also approved a concept to upgrade infrastructure and methodological support for environmental epidemiology studies. The concept was presented by Kimberly Gray, Ph.D., a health scientist administrator in DERT.

The council also received updates from John Balbus, M.D., NIEHS senior advisor on public health, regarding the NIEHS Global Environmental Health (GEH) program. Mike Humble, Ph.D., also in DERT, briefed the group on the Undergraduate Research Education Program (UP), which is designed to enhance diversity in the environmental health sciences (see [story](#)).

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



NIEHS and National Toxicology Program Director Linda Birnbaum, Ph.D., relayed potentially good budget news — the American Cures Act could bring NIH an additional \$10 billion over the next five years. “It’s got a fairly good chance of moving forward [in Congress],” she said, “so we are guardedly hopeful.” (Photo courtesy of Steve McCaw)



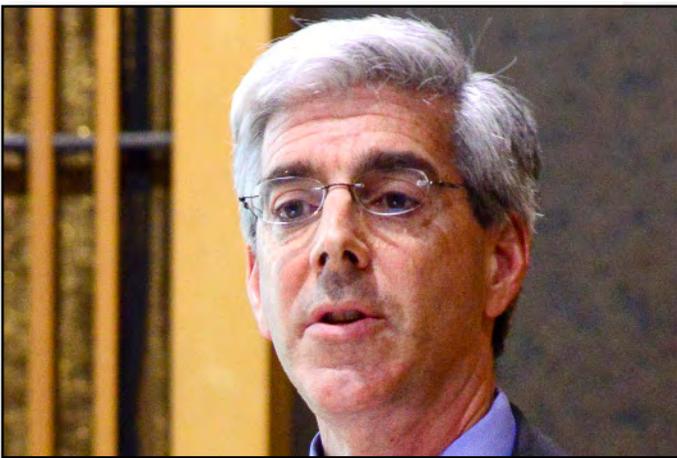
*Wilcox (see [text box](#)), a senior investigator in the NIEHS Epidemiology Branch, presented the science talk to the council. He is past president of the American Epidemiological Society and the Society for Epidemiologic Research, and until recently, he was editor in chief of the journal *Epidemiology*. (Photo courtesy of Steve McCaw)*



In making the case for upgrading support for environmental epidemiology studies, Kimberly Gray, Ph.D., health scientist administrator of DERT, noted that NIEHS supported development, study, or maintenance activities for 58 such studies in fiscal years 2013 and 2014. (Photo courtesy of Steve McCaw)



Council members Tomas Guilarte, Ph.D., from Columbia University, and Linda McCauley, Ph.D., from Emory University, were active participants in discussions. (Photo courtesy of Steve McCaw)



Balbus, who directs the NIEHS-World Health Organization Collaborating Centre for Environmental Health Sciences, said that from FY2012-FY2014, NIEHS supported 157 GEH research projects around the world. (Photo courtesy of Steve McCaw)



Mary Gant, who has been the NIEHS Legislative Liaison in Washington, D.C. since 1987, is retiring at the end of July. Birnbaum led meeting attendees in a warm round of applause in appreciation of Gant's service. (Photo courtesy of Steve McCaw)

Epidemiology: partnering with basic science by looking at the big picture

That was the mundane title of what turned out to be an amusing, enlightening, and rather provocative scientific talk given by Allen Wilcox, M.D., Ph.D., during the meeting.

Wilcox presented data from two research pursuits over the course of his 35-year career as a scientist at NIEHS — genetics and epigenetics, and fertility and reproduction. He showed how epidemiologic findings could raise a host of questions about fundamental biology.

For example, new data show a connection between a mother's age and gene methylation in her newborn, suggesting the possibility of undiscovered mechanisms of methylation.

“Let's talk about sex.” With a phrase one doesn't often hear in scientific presentations, Wilcox introduced his important findings on fertility and pregnancy, including data on how long sperm survive in the female reproductive tract, and information about a potential relationship between intercourse and the timing of women's menstrual cycles, particularly ovulation.

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Tox21 tools promoted at UC Davis meeting

By Virginia Guidry

A delegation of scientists from NIEHS and the National Toxicology Program (NTP) promoted high throughput screening tools at a meeting June 18-19 at the University of California, Davis. Led by NIEHS and NTP Director Linda Birnbaum, Ph.D., they joined a number of high-profile NIEHS grantees (see [text box](#)), discussing use of the innovative methods for identifying environmental toxicants.

The event, “Elucidating Environmental Dimensions of Neurological Disorders and Diseases: Understanding New Tools from Federal Chemical Testing Programs,” was organized by the Environmental Defense Fund (EDF) in partnership with NIEHS, NTP, and the U.S. Environmental Protection Agency (EPA).

“The overall goal was to introduce these tools to researchers who might not be familiar with them,” said Kris Thayer, Ph.D., NTP deputy director for analysis.



“The purpose of Tox21 is to support the evolution of toxicology from a mostly observational science to a predominantly predictive science focused upon mechanism-based, biological observations,” Birnbaum said. (Photo courtesy of Christopher Portier)

Faster testing for toxic effects

The [Tox21](#) program, a collaboration involving NTP, EPA, National Institutes of Health Chemical Genomics Center, and the U.S. Food and Drug Administration, uses high throughput screening (HTS) to research and test chemicals of toxicological concern. The automated approach provides a rapid and low cost method of systematically testing the impacts of many chemical compounds at varying concentrations on cells and model tissues.

Birnbaum outlined three main goals of Tox21:

- Prioritize chemicals needing further study
- Identify mechanisms contributing to toxicity
- Develop models to test biological response in humans

Linked video: (Launches in new window)

[Watch a video of the high-speed robot screening system for the Toxicology in the 21st Century initiative, a collaboration of the National Institutes of Health, EPA, and the Food and Drug Administration \(03:16\).](#)

Download Media Player: Flash

After potential toxicants are identified, toxicologists can use observational studies and systems biology approaches to explore how dose and timing of exposure contribute to toxicity.

Putting HTS into action

In addition to background from Birnbaum and NTP Associate Director John Bucher, Ph.D., presenters described HTS assays in detail and lessons learned by researchers thus far. Some attendees also participated in what organizers described as genius bars, where they received step-by-step instructions on accessing Tox21 tools. Instructors included experienced researchers such as NTP molecular toxicologist Scott Auerbach, Ph.D., and Nisha Sipes, Ph.D., of the NTP Biomolecular Screening Branch.

To encourage junior researchers to learn about and use the HTS tools, NTP provided eight travel awards to basic scientists outside of the federal government. One of the awardees, Merja Jaronen, Ph.D., research fellow at Brigham and Women's Hospital and Harvard Medical School, remarked, "I am about to test some of the compounds in a zebrafish model of neurodegeneration, and it was extremely interesting, as well as valuable, to learn about the databases and see how other people have benefited from these tools."

Providing resources and moving forward

Another hallmark of Tox21 is that the data are available to researchers in publicly available databases, with multiple search capabilities. For example, NTP provides a library of compounds that impact neural cells. "The 80 compounds include known developmental neurotoxicants as well as chemicals of environmental interest, such as flame retardants and polycyclic aromatic hydrocarbons," Birnbaum said.

A number of new developments are on the horizon for Tox21. Researchers plan to increase the use of normal human cells in testing. There is emphasis on measuring impacts on messenger ribonucleic acids (RNA), also called transcriptomics, because of RNA's role in transcribing genetic information for protein synthesis.

The goal is to select more than 1,500 sentinel human genes that have full pathway coverage and can predict the gene expression of the rest of the transcriptome with high accuracy, dubbed the Human S1500 Gene Set, for use in HTS. To parallel the 1500 sentinel human genes (S1500), a mouse S1500 and a zebrafish S1500 are also under development.

(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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Speakers and Moderators

- Leonard Abbeduto, Ph.D, UC Davis MIND Institute
- Scott Auerbach, Ph.D., NTP
- Tina Bahadori, Ph.D., EPA
- Linda Birnbaum, Ph.D, NIEHS
- Jeffrey Bronstein, M.D., Ph.D., UC Los Angeles
- John Bucher, Ph.D., NTP
- Thomas Burke, Ph.D., EPA
- Elaine Faustman, Ph.D., University of Washington
- Irva Hertz-Picciotto, Ph.D., UC Davis
- Keith Houck, Ph.D., EPA
- Valerie Hu, Ph.D., George Washington University
- Seth Kullman, Ph.D., North Carolina State University
- Pamela Lein, Ph.D., UC Davis
- Matt Martin, Ph.D., EPA
- Jennifer McPartland, Ph.D., EDF
- Craig Newschaffer, Ph.D., Drexel University
- Chirag Patel, Ph.D., Harvard University
- Heather Patisaul, Ph.D., North Carolina State University
- Christopher Portier, Ph.D., EDF
- Francisco Quintana, Ph.D., Harvard University
- Robert Ring, Ph.D., Autism Speaks
- Peter Schmidt, Ph.D., National Parkinson Foundation
- Gina Solomon, M.D., California Environmental Protection Agency
- Robert Tanguay, Ph.D., Oregon State University
- Caroline Tanner, M.D., Ph.D., San Francisco Veteran's Affairs Medical Center
- Kristina Thayer, Ph.D., NTP
- Russell Thomas, Ph.D., EPA
- Ray Tice, Ph.D., NTP (Retired)
- Sarah Vogel, Ph.D., EDF

Scholars Connect kicks off fourth year of boot camp

By Eddy Ball

The NIEHS Scholars Connect Program (NSCP) welcomed five new recruits June 8 to its weeklong boot camp and orientation. Classroom sessions and hands-on training in scientific method and laboratory procedures marked the start of the fourth round of a yearlong immersion into scientific research experience for students at local universities and historically black universities and colleges.

NSCP is a program run by the [NIEHS Office of Science Education and Diversity \(OSED\)](#), headed by Ericka Reid, Ph.D. OSED provides innovative training for teachers in K-16 science education, trains aspiring students from underrepresented populations, and engages minority students and communities throughout the U.S. (see [text box](#)).

The program is part of an institute-wide effort towards meeting the NIEHS strategic plan goal of increasing diversity among scientists in the environmental health sciences. Though relatively new, it has already served as the model for a new program of training grants announced earlier in June (see [story](#)).

Fine tuning a model for boosting success rates in science education

During the orientation, Reid and NSCP coordinator Erica Rogers, Ph.D., discussed details of the boot camp and the yearlong training program ahead.

“We are offering students the opportunity to learn more about their disciplines – you’re all STEM [science, technology, engineering, and mathematics] majors,” Reid explained, “and more specifically, the environmental health sciences, which is our focus.”

Reid shared a video of a 2013 TED talk by a pioneer in new approaches to scientific education, Freeman Hrabowski, Ph.D., president of the University of Maryland, Baltimore County (UMBC).

UMBC is the home of the Meyerhoff Scholars Program, which began in 1988, with generous support from philanthropists Robert and Jane Meyerhoff, to provide financial assistance, mentoring, advising, and research experience to African-American male undergraduate students committed to obtaining Ph.D. degrees in math, science, and engineering. Hrabowski was provost at UMBC when the Meyerhoffs offered to fund the program, and continued his award-winning work with the program when he was appointed president in 1992.



Returning scholar Carri Murphy, a senior at North Carolina Central University, will continue her work for a second summer with lead researcher Mike Resnick, Ph.D., staff scientist Daniel Menendez Rendon, Ph.D., and biologist Joyce Snipe in the NIEHS [Chromosome Stability Group](#). (Photo courtesy of Steve McCaw)



Linked video:
[Watch as Hrabowski outlines the Four Pillars of Success in Science and describes his university's measures to redesign courses in science and liberal arts \(15:10\)](#)
(Launches in new window)

Download Media Player:  Flash 

With the Meyerhoff Scholars Program as an inspiration, Reid oversaw creation of NSCP in 2010 with three broad aims to ensure greater success for students with diverse backgrounds.

- Emphasize a high quality scientific research experience to engage students.
- Offer career exploration activities to help students form goals based on realistic scenarios.
- Provide a network of student support that includes multiple mentors, colleagues, fellow participants, and OSED staff.

NSCP can already boast of enviable outcomes, with former participants accepted into graduate programs at North Carolina A&T State University, North Carolina Central University, Campbell University, Liberty University, and Northwestern University. Last year's winner of the first NSCP Outstanding Scholar Award, Carri Murphy, was invited to return for a second summer to work in her mentor's lab prior to her graduation this December from North Carolina Central University.

(Eddy Ball, Ph.D., is a contract writer with the NIEHS Office of Communications and Public Liaison.)



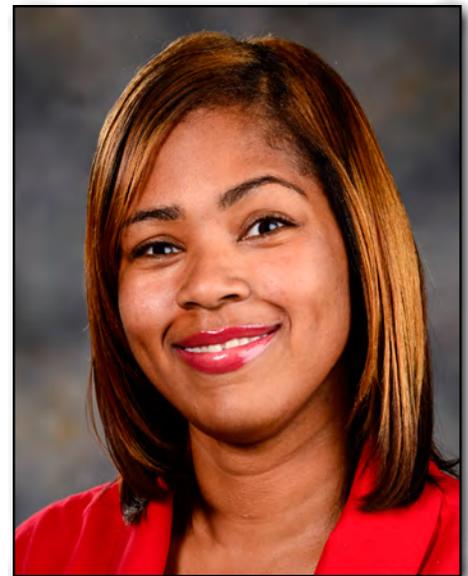
Fellow North Carolina Central University senior Tobias Flow will receive mentoring from National Toxicology Program (NTP) toxicologist Michael Sanders, Ph.D., and postdoctoral fellow Gabriel Knudsen, Ph.D., as part of the Toxicology and Toxicokinetics Group headed by NIEHS and NTP Director Linda Birnbaum, Ph.D. (Photo courtesy of Steve McCaw)



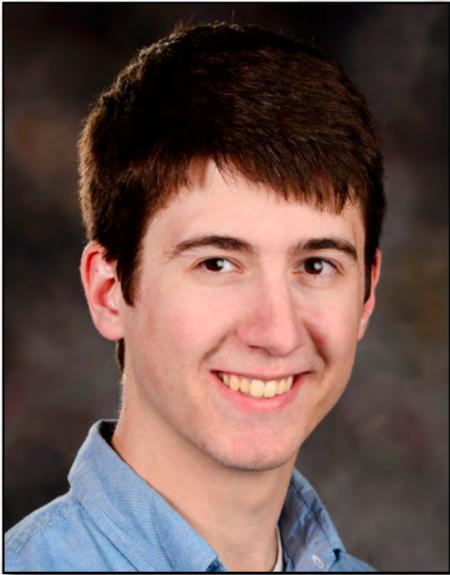
Porscha Walton, a senior at St. Augustine's University, will spend her year as an NSCP participant working with the NTP [Office of Health Assessment and Translation](#) headed by Kris Thayer, Ph.D. (Photo courtesy of Steve McCaw)



Assigned to the NIEHS [Clinical Research Unit](#), North Carolina State University junior Maura Schwartz will conduct her project under the direction of associate medical director Shepherd Schurman, M.D. (Photo courtesy of Steve McCaw)



Also a senior at North Carolina Central University, Alanna Burwell joins the NTP [Molecular Pathogenesis Group](#), working with group leader Darlene Dixon, D.V.M., Ph.D., and biologist Linda Yu. (Photo courtesy of Steve McCaw)



Lucas Van Gorder, a junior majoring in genetics at North Carolina State University, will join Chip Romero, Ph.D., and Negin Martin, Ph.D., in the Neurobiology Laboratory Viral Vector Core. (Photo courtesy of Steve McCaw)



While most of the workshop involves hands-on and small group instruction in the lab, the students spent a few hours in a more traditional classroom setting. Shown, from left, are Burwell, Walton, and Schwartz. (Photo Courtesy of Steve McCaw)



At the bench, volunteers gave generously of their time to introduce students to techniques, such gel electrophoresis, that they will be using for their projects. Shown, left to right, are NTP mentor Yu and Molecular Genetics Laboratory technician Joetta Hitchcock-Smith. (Photo courtesy of Steve McCaw)



Rogers lined up mentor assignments for the students and volunteer instructors for the boot camp. (Photo courtesy of Steve McCaw)



Reid joined Rogers for the classroom component of the boot camp training. OSED's intensive mentoring model and stipend support helped inspire a new extramural grant program to increase diversity in the biomedical workforce. (Photo courtesy of Steve McCaw)

NIEHS reaches out to help STEM students pass the torch

By Geoffrey Feld

In addition to bringing students to NIEHS, OSED reaches out to local schools to support science education. At Athens Drive High School in Raleigh, North Carolina, seniors in Shane Barry's advanced science, technology, engineering, and mathematics (STEM) class concluded their capstone research projects (see [story](#)) May 18-29 with detailed presentations. In April, the groups working on the capstone projects selected three volunteers from NIEHS — fellow Geoffrey Feld, Ph.D.; and contractors Kenda Freeman and Sara Mishamandani — to serve as mentors, who collaborated with their groups and attended the presentations.

Barry encouraged audience members to ask questions throughout the talks, and he questioned the students in the Socratic method, to encourage critical thinking. The resulting presentations delved deeper into the projects than PowerPoint slides alone could have achieved. Barry explained that this approach helps groom students for STEM career paths, where venture capitalists and regulators may question them in a similar manner.

The students showed themselves to be quick-thinkers who have become experts on particular aspects of their research. Barry invited fellow teacher Megan Myers to bring her freshman English class to the presentation on hydraulic fracturing and water safety. The younger audience members, who may also conduct capstone projects of their own in a few years, tested the seniors' knowledge with informed questions on the topic. The team proposed a practical solution to water problems caused by fracking, involving reasonable upgrades to local water treatment plants to handle the possible introduction of fracking-derived 1,4-dioxane.

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

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NIEHS marks advances in diversifying the biomedical workforce

By Eddy Ball

NIEHS celebrated two milestones this month in its ongoing efforts to increase diversity in the biomedical workforce through innovative training initiatives.

During the June 2 open session of the [National Advisory Environmental Health Sciences Council](#), Michael Humble, Ph.D., health scientist administrator in the NIEHS Division of Extramural Research and Training, outlined six new awards made April 1 as part of the Undergraduate Research Education Program (UP) to Enhance Diversity in the Environmental Health Sciences.



Humble began his talk with a reference to Goal 9 of the NIEHS strategic plan, which calls for training the next generation of environmental health science leaders from a wider range of scientific disciplines and diverse backgrounds. (Photo courtesy of Steve McCaw)

The following week, the NIEHS Scholars Connect Program welcomed its fourth cohort of students (see [story](#)) and recognized the exceptional achievements of previous participants in the yearlong training program.

“NIH as a whole is committed to really increase the diversity in the biomedical workforce,” said NIEHS and National Toxicology Program Director Linda Birnbaum, Ph.D. “Trying to do something different, we hope, will lead to [even more] positive outcomes.”

New life for science curricula

UP and Scholars Connect both got their inspiration from several programs, including the following:

- The National Institute of General Medical Sciences (NIGMS) Maximizing Access to Research Careers Undergraduate Student Training in Academic Research (U-STAR) program, where underrepresented undergraduate students, typically in their junior and senior years of college, are provided two-year research and training opportunities in the biomedical sciences.
- The [Meyerhoff Scholars Program](#) at the University of Maryland, Baltimore County, where science education has been fundamentally revised to improve success rates.

The universities receiving the new grants have several basic strategies in common:

- Targeting students from underrepresented populations, with a 2:1 or greater ratio between mentors and the 5-8 students in each program, with long-range state-of-the-art research projects in the environmental health sciences.
- Providing full-time stipend support during the summer months and part-time support during the academic year, leveraging existing NIEHS programs and resources for greater impact, and integrating research experience with coursework, seminars, and social networking.
- Using Individual Development Plans for participants, objective-based program evaluations, and long-term tracking for measuring participant and program outcomes.



Council members David Eaton, Ph.D., left, of the University of Washington, and Guilarte, center, represent institutions with UP training grants. (Photo courtesy of Steve McCaw)



Birnbaum, right, expressed her confidence that the new approach would advance diversity. Gwen Collman, Ph.D., left, director of the NIEHS Division of Extramural Research and Training, was obviously proud of her staff's work in putting together the program and facilitating funding. (Photo courtesy of Steve McCaw)

Win-win for students, NIEHS programs, and the future

During his presentation, Humble described the benefits of this new approach. “It’s a great opportunity for students to fully engage in a project and then return to school,” he said. “It’s a nice way to build on [resources and talent] that we already have in place.”

The council gave its early concurrence for UP during its September 2014 meeting. This time, members expressed satisfaction with the framework Humble and the NIEHS team developed for the program.

Council member and grantee Tomas Guilarte, Ph.D., of Columbia University, pointed to ways UP could increase the number of qualified candidates from underserved populations for faculty positions in the future. “We [desperately] need to build a pipeline,” he said, referring to a recent experience trying to fill an open position at Columbia.

He added that he was also delighted at recruitment so far and that he was looking forward to being one of the 17 faculty mentors in the Columbia program.

(Eddy Ball, Ph.D., is a contract writer with the NIEHS Office of Communications and Public Liaison.)

Recipients of Undergraduate Research Education Program (UP) to Enhance Diversity in the Environmental Health Sciences Grants

Six university and program consortia that received funding include:

- California State University Northridge and the University of California, Los Angeles – Student-to-Scientist Bridge Program in Environmental Health Science (S2S Bridge)
- Columbia University and John Jay College — Undergraduate Research Program to Promote Diversity in EHS (Environmental Health Sciences)
- Northeastern University – Research Opportunities for Undergraduates: Training in Environmental Health Sciences (ROUTES)
- University of Arizona (UA) – UA Environmental Health Transformative Research Undergrad Experience (EH TRUE)
- University of Colorado, Denver – Colorado Undergraduate Research in Environmental Health Sciences
- University of Washington – Supporting Undergraduate Research Experiences in Environmental Health (SURE-EH)

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Tell the Environmental Factor what you think

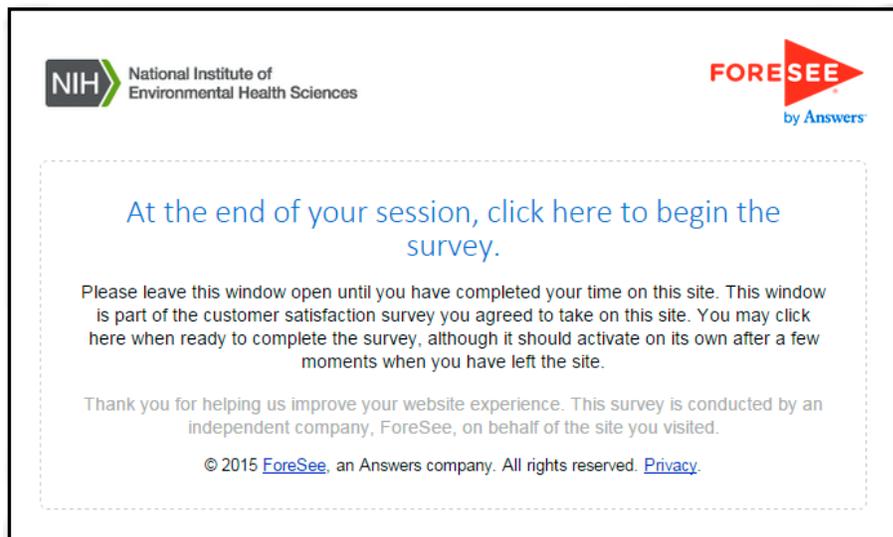
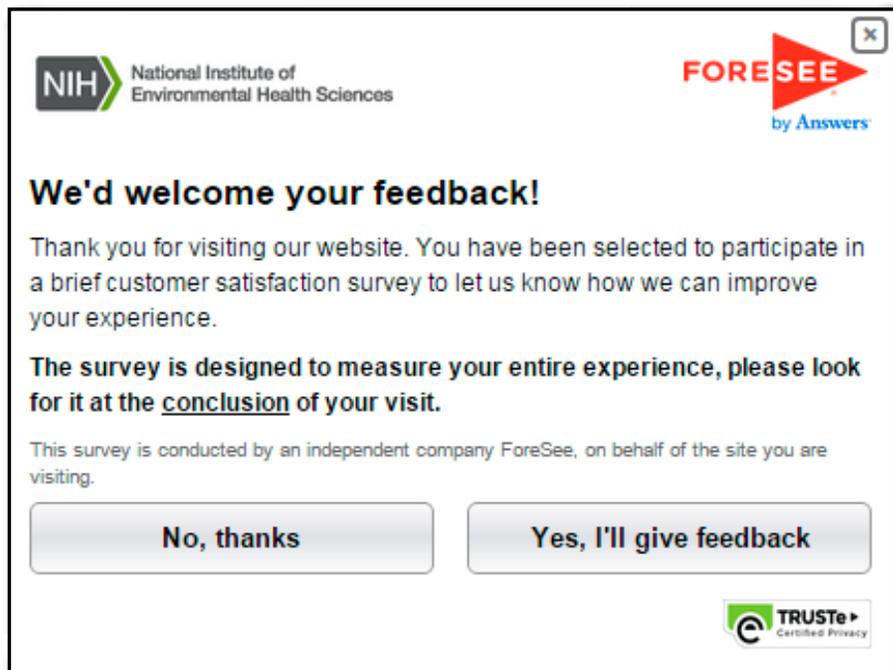
By Kelly Lenox

The Environmental Factor staff is always working to improve our readers' experience. We want to know what you think about the newsletter, so we invite you to share your thoughts and opinions by completing a short survey.

When the pop-up window appears (see image, top right), please choose "Yes, I'll give feedback." After you finish your reading and close the newsletter, you'll be prompted in a new browser window, like the one bottom right, to complete the survey.

ForeSee surveys are used on many websites, but these questions are specific to NIEHS. This is the first time we've used a survey to gauge the effectiveness of the Environmental Factor. Our goal is to produce a newsletter that broadens your knowledge of environmental and health research. We hope you will participate and look forward to reviewing your thoughtful responses.

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Ethics Day marks sixth year with presentation by Nobel laureate

By Eddy Ball

NIEHS turned out for a June 4 standing-room only Ethics Day event, which also marked the institute's emergence as leader in government ethics (see [text box](#)).

The event featured a talk by Nobel Prize winner Oliver Smithies, D. Phil., on "Ethical Behavior: A Moving Target," preceded by an overview of government ethics by moderator Bruce Androphy, J.D., head of the award-winning NIEHS Ethics Office, and an introduction by Deputy Director Rick Woychik, Ph.D.

As always, Ethics Day featured healthy doses of humor from Androphy, both in his opening remarks and during the Ethics Survivor team competition.

Challenging weak assumptions

A distinguished professor at the University of North Carolina at Chapel Hill, Smithies brought a fresh and often humorous perspective to his take on scientific ethics. Although he touched on familiar topics, such as the treatment of human subjects, Smithies also took an especially close look at the sins of commission and omission when communicating scientific results.

Speaking to an audience that included some of the leading and most productive scientists at NIEHS, Smithies opened with a reference to truth in advertising and a strong challenge to his audience. “We need truth in science,” he said, “[but] we don’t have it.”

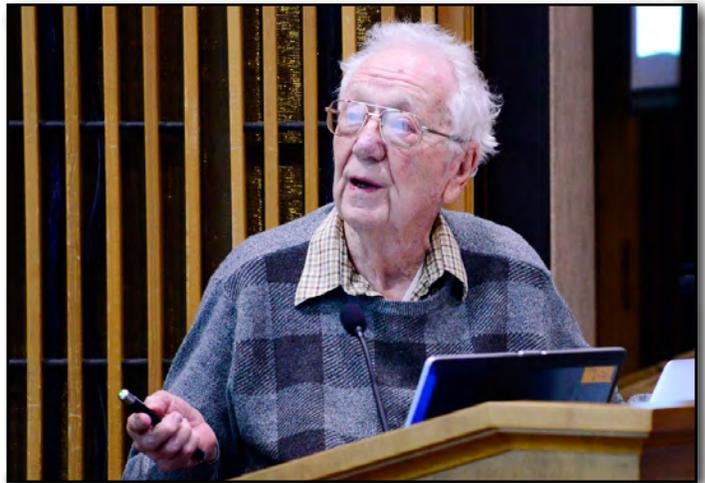
Many scientists, he explained, simply exaggerate the significance of their results and craft misleading titles for their articles. According to Smithies, the bar for statistical significance is set much too low at $P < 0.05$, which means there is less than a 5 percent probability that the observed results were due to chance, rather than a real effect.

He criticized scientists who increase their number of subjects until they manage to meet the $P < 0.05$ standard, neglect to specify the exact P value achieved or the presence of negative results, or cut off experiments prematurely to maintain a deceptive statistical significance.

From sins of omission to outright theft and fraud

From that most common of scientific shell games, Smithies went on to list several more ways scientists fail to be transparent, from refusing to acknowledge earlier results from other researchers, to hiding results until the scientist can take full credit for a discovery. He pointed to Galileo’s deceptive description of his observation in 1610 that Venus circles the sun based on charting phases of the moon.

More serious behaviors, such as fabrication of results or manipulation of data, are usually easier to detect because the findings cannot be replicated, he said. Smithies also pointed to plagiarism, which can be tracked down quickly by computer programs and is easy to avoid with minimal effort.



Smithies reinforced sound advice on transparency in science with his series of charmingly simple handwritten slides. “You’ll find it’s easy and enjoyable to quote other people’s work.” (Photo courtesy of Steve McCaw)



Representing the NIEHS Ethics Office, Androphy, right, with Fischmann, as the NIEHS ethics program joined the ranks of the best of the best in government ethics across HHS. (Photo courtesy of Bruce Androphy)



Woychik was one of several ranking members of leadership on hand for the talk. Not shown are Associate Director of Management Joellen Austin and Deputy Associate Director of Management Chris Long. (Photo courtesy of Steve McCaw)

“[Some] ethical behavior changes with time,” Smithies said, touching on the moving target aspect of ethics. He pointed to changes in public attitudes toward segregation and male dominance, as well as toward once highly controversial medical procedures that are now widespread, such as *in vitro* fertilization.

Smithies flavored his generalities with recent examples, as well as references to such famous scientific pioneers as Robert Koch, Louis Pasteur, and Gregor Mendel. “Humans don’t change very much [through time],” he explained. “Scientists are no better than anyone else.”

(Eddy Ball, Ph.D., is a contract writer with the NIEHS Office of Communications and Public Liaison.)



In the audience or at the podium, Androphy, center, was always ready to hear or tell a good joke or humorous story. Seated behind him, biologist Maggie Humble, center, and postdoctoral fellow Monica Frazier, Ph.D., joined in the appreciation of Smithies’ sharp wit. (Photo courtesy of Steve McCaw)



Although scientists made up the majority, the audience included people from across NIEHS, a testament to the wide respect for Smithies. (Photo courtesy of Steve McCaw)



Whether Smithies was serious or light hearted, he kept members of the audience, such as Joan Pakenham, Ph.D., center, director of the Office of Human Research Compliance, engaged with his talk. (Photo courtesy of Steve McCaw)



As the smile on the face of the normally serious NIEHS Bioethicist David Resnik, J.D., Ph.D., indicated, fewer people hardly translated into less laughter. Androphy’s quips and easy laughter proved to be infectious. (Photo courtesy of Steve McCaw)



The audience was considerably smaller and the setting more intimate for the Ethics Survival game. (Photo courtesy of Steve McCaw)



NIEHS Ethics Coordinator Jackie Stillwell clearly appreciated the absurdity of some of the multiple choice items on Androphy's ethics quiz. (Photo courtesy of Steve McCaw)

Setting a standard for best practices

This spring, the NIEHS Ethics Office was honored with the 2015 Ethics Program Innovation Award in Recognition of Innovative Ethics Education and Communication Practices for its Ethics Day program.

During an April 28 ceremony, Androphy received the award from the U.S. Department of Health and Human Services (HHS) Acting Associate General Counsel and Designated Agency Ethics Official Elizabeth Fischmann, J.D. The event was part of the Deputy Ethics Counselor Workshop held in the Lister Hill Auditorium on the National Institutes of Health Campus in Bethesda, Maryland.

With the appointment of Androphy in 2009 by NIEHS and National Toxicology Program Director Linda Birnbaum, Ph.D., while she was still in her first year at the helm, the NIEHS Ethics Office intensified its education of institute employees and committed to assisting them in navigating the myriad ethics laws, rules, and regulations. From the start, Birnbaum has led by example, giving the Ethics Office her full support.

Today, the NIEHS Ethics Office can boast of its efforts to ensure public trust in the institute's integrity, as well as of its award-winning programs to educate employees about how the office can help them avoid any perception of conflict of interest.

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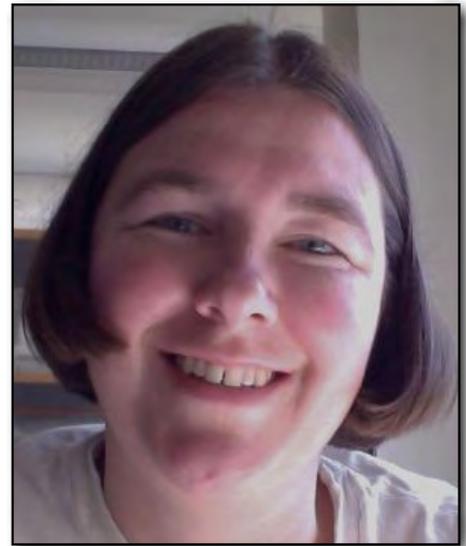
Seven promising Superfund trainees receive K.C. Donnelly award

By Sara Mishamandani

Seven exceptional NIEHS-funded Superfund Research Program (SRP) trainees received a 2015 [K.C. Donnelly Externship Award Supplement](#) to enrich their research in environmental health science.

Now in its fifth year, the annual award was established to honor environmental health researcher and longtime SRP grantee Kirby (K.C.) Donnelly, Ph.D., who died in 2009 after a distinguished career with the Department of Environmental and Occupational Health at Texas A&M University.

Kate Buckman, Ph.D., is a postdoctoral research associate at the Dartmouth College Superfund Research Program (SRP) Center under the guidance of Celia Chen, Ph.D. Buckman studies the effects of temperature, salinity, and organic carbon on methylmercury bioaccumulation in estuarine organisms and conducts fieldwork across estuarine and open water systems. During her externship at the U.S. Environmental Protection Agency (EPA) lab in Narragansett, Rhode Island, Buckman will evaluate using killifish to link mercury exposure to ecologically relevant outcomes, under the mentorship of Diane Nacci, Ph.D., from the Population Ecology Branch of the EPA's Atlantic Ecology Division.



“Working with Dr. Nacci at the Narragansett EPA laboratory will allow me to learn new techniques and skills and establish a collaborative research project that takes advantage of the facilities, expertise, and support available within the Atlantic Ecology Division of the EPA,” Buckman said. (Photo courtesy of Kate Buckman)

Marvic Carmona De Jesus is a graduate student under the guidance of Ingrid Padilla, Ph.D., at the University of Puerto Rico in Mayaguez, which is part of the Northeastern University SRP Center. He is assessing and quantifying the fate and transport of dense nonaqueous phase liquids in karst groundwater systems. His externship at the Oregon State University (OSU) SRP Center, under the guidance of Kim Anderson, Ph.D., will involve using passive sampling devices to detect, monitor, and quantify contaminants in water. He will apply the skills he learns to the karst region of northern Puerto Rico.

Lisandra Santiago Delgado is a graduate student under the guidance of Staci Simonich, Ph.D., at the OSU SRP Center, where she researches remediation of polycyclic aromatic hydrocarbons (PAHs). For her externship at the EPA Robert S. Kerr Environmental Research Laboratory, in Ada, Oklahoma, Delgado will work with EPA hydrologist Eva Davis, Ph.D., on thermally remediating Superfund soils contaminated with PAHs. Techniques include steam injections and quantification of PAHs and toxicity in the soil before and after remediation.



“The K.C. Donnelly Externship will enable me to advance my knowledge and develop new skills to advance our understanding of environmental health and engineering issues faced by the people of Puerto Rico, a population with a large burden of health disparities,” said Carmona. (Photo courtesy of Marvic Carmona De Jesus)



“This externship will provide me with an opportunity to enhance my capabilities as an independent researcher in environmental health sciences. I am excited to work with Dr. Davis, who is an expert in the field of thermal remediation,” Santiago Delgado said. (Photo courtesy of Lisandra Santiago Delgado)



“The K.C. Donnelly Externship will not only help me foster further collaborative relationships with Dr. Stegeman and other members at WHOI, but it will also provide me with the opportunity to learn and apply cutting-edge techniques in the increasingly important field of bioinformatics,” Fritsch said. (Photo courtesy of Erika Fritsch)

Erika Fritsch, Ph.D., a postdoctoral fellow at the University of California (UC), Davis SRP Center, studies the effects of polychlorinated biphenyls (PCBs) on the ryanodine receptor (RyR) in killifish, under the guidance of Isaac Pessah, Ph.D. This receptor is essential to neuron signaling and health and may play a role in the neurotoxic mechanism associated with PCBs. At Woods Hole Oceanographic Institute (WHOI) in Massachusetts, Fritsch will work with John Stegeman, Ph.D., who is part of the Boston University SRP Center. Fritsch will use the bioinformatics expertise she develops to help to establish fish as models for RyR toxic endpoints.

Celebrating a renowned mentor and scholar

Donnelly was a dedicated mentor to his students and postdoctoral researchers, instilling the importance of applying knowledge and findings to improve the health of communities exposed to environmental contaminants. To honor Donnelly, the award supports SRP graduate students and postdoctoral fellows who are pursuing transdisciplinary research and emphasizes the importance of research application and collaboration to promote human health.

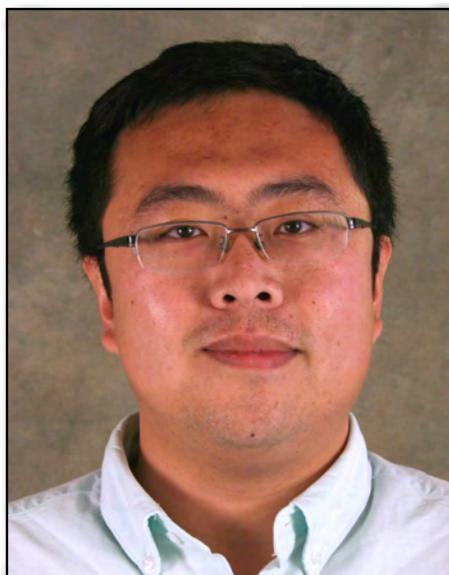
The award provides each SRP trainee with up to \$10,000 for supplies, travel, housing, and costs for up to three months of research, training, and collaboration at other SRP centers, government laboratories, and state, local, or tribal agencies.

Zhilin Guo is a graduate student under the mentorship of Mark Brusseau, Ph.D., at the University of Arizona SRP Center. Guo is exploring factors that affect groundwater remediation of hazardous waste sites contaminated with chlorinated solvents. During her externship at the UC Davis SRP Center, under the guidance of Graham Fogg, Ph.D., Guo will work toward solving current research problems related to plume persistence, which has been observed in many field sites. This advancement will enhance site characterization and site management for contaminated sites with large groundwater plumes.

Miao Li, a graduate student at the University of Iowa SRP Center, investigates the mechanism of toxicity of airborne PCBs by the formation of protein adducts, under the mentorship of Gabriele Ludewig, Ph.D. He will expand that research through an externship at the University of California, Berkeley Center with Daniel Nomura, Ph.D. Li will learn methods to identify protein targets for PCB metabolites, to help reveal mechanisms involved in the toxicity of airborne PCBs.



“The supplement provides an opportunity for me to learn an advanced numerical flow and transport program, which will enrich my current research and improve my understanding of how media impacts contaminant transport behavior,” said Guo. (Photo courtesy of Zhilin Guo)



“The University of California, Berkeley provides an ideal environment for the externship, with cutting edge techniques and state-of-the-art instruments,” said Li. (Photo courtesy of Miao Li)



“In addition to completing my project that focuses on gene transfer, I will gain a greater understanding of dechlorinating communities and methods of monitoring intercellular interactions,” said Redfern. (Photo courtesy of Lauren Redfern)

Lauren Redfern, a graduate student in the Duke University SRP Center under the guidance of Claudia Gunsch, Ph.D., focuses on microbial communities and their potential for bioremediation at Superfund sites. She will travel to the University of California, Berkeley SRP Center to evaluate microbial interactions, under the mentorship of Lisa Alvarez-Cohen, Ph.D. During her externship, Redfern will determine what biogeochemical influences enhance gene transfer between bacterial species to result in increased degradation rates. These results will expand our understanding of horizontal gene transfer as a bioremediation technique.

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

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Public forum highlights progress on replacing animals used in safety testing

By Catherine Sprankle

Members of the [Interagency Coordinating Committee on the Validation of Alternative Methods](#) (ICCVAM) discussed alternatives for chemical and product safety testing during a May 27 [public forum](#) at the National Institutes of Health in Bethesda, Maryland. Participants discussed subjects such as transparency in industry’s reporting of animal use, training for regulators on available nonanimal methods and strategies, and communication with the public on the science behind nonanimal methods.

Twelve public participants and nearly 100 webcast viewers, representing interest groups from industry, academia, and animal welfare organizations, joined 15 committee members at the event. [The National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods](#) (NICEATM) organized the meeting (see [sidebar](#)).

Agencies highlight ongoing activities

ICCVAM co-chair Anna Lowit, Ph.D., from the U.S. Environmental Protection Agency (EPA), reviewed the committee’s current priority areas and highlighted progress in development of a nonanimal testing strategy to identify skin sensitizers.

Lowit also described EPA’s work with pesticide manufacturers to implement alternative tests or waive tests completely. Referring to the nearly 600 test waivers granted over the last four years, Lowit noted, “We estimate that [these account for] upwards of 50,000 animals not used and over \$100 million to industry saved.”

In his summary of NIEHS activities, ICCVAM representative [Nigel Walker, Ph.D.](#), cited the [West Virginia chemical spill](#) as an example of how nonanimal methods can speed the assessment of health hazards presented by a complicated environmental event. “This is not something where we can take 10 years and [evaluate chemical toxicity] robustly over a long period of time,” he said. “People want an answer relatively quickly, to allay any fears and determine whether the screening level was appropriate.”



Lowit provided updates on ICCVAM goals for fiscal year 2015. (Photo courtesy of NIH)

Stakeholders address education and tracking progress

Some public comments focused on a request by ICCVAM for suggestions on how to track progress towards replacement, reduction, and refinement of animal use. An online viewer noted that current U.S. law does not require collection of data on use of rats and mice and asked if there was potential for that to change. Other commenters expressed concern about how to assure the public that nonanimal methods would adequately protect public health.

There were also questions about training and education opportunities for both potential users of new test methods and regulators evaluating test submissions, which allowed representatives of several agencies to highlight training and educational resources currently available.

Lowit invited stakeholders to continue to engage ICCVAM both in meetings and through more informal interactions.

Slides from the event and a recording of the webcast are [available on the NTP website](#). ICCVAM will provide another update in September at the annual meeting of the [Scientific Advisory Committee on Alternative Toxicological Methods](#).

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. **Congress established** the following groups to ensure the involvement of all stakeholders in the development of such methods.

- **Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM)** — coordinates the activities of member federal agencies to replace, reduce, or refine animal use.
- **NTP Interagency Center for the Evaluation of Alternative Methods (NICEATM)** — an office within the National Toxicology Program (NTP) that supports ICCVAM activities and NTP high-throughput screening projects. The center is involved with development of novel approaches to testing.
- **Scientific Advisory Committee on Alternative Toxicological Methods (SACATM)** — advises NICEATM, ICCVAM, and the NIEHS and NTP director. Representatives are drawn from industries regulated by ICCVAM member agencies, animal welfare organizations, academia, test method developers, and regulatory agencies outside of the federal government.



Casey summarized recent NICEATM activities and publications for participants in the public forum. (Photo courtesy of NIH)



Walker discussed alternative methods to assess toxicity of flame retardants, and collaborations with small business test method developers. (Photo courtesy of NIH)



A webcast at the public forum allowed another 100 or so stakeholders to participate remotely. (Photo courtesy of April Bennett)

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

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Innovative training program launched in the wake of Ebola

By Eddy Ball

The NIEHS Worker Training Program (WTP) did what it does best at a grantee meeting May 28 in Research Triangle Park, North Carolina. WTP brought together veteran worker-safety training experts to discuss training needs for future infectious disease outbreaks, ranging from influenza and Ebola hemorrhagic fever to newly emerging biological threats.

The innovative approach targets workers beyond direct health care providers, to train others who might be affected by an infectious disease outbreak, from lab techs and janitors, to garbage handlers, first responders, and morticians.

Moderated by [WTP](#) Director Chip Hughes, more than 20 representatives from awardees (see [text box](#)) of grants totaling some \$650,000 came together to plan awareness, operations, and community training sessions across the U.S., which must be in place by July 31, 2015.



Hughes moderated the discussions about biosafety training. WTP staffers Sharon Beard, Jim Remington, and Ted Outwater also participated in planning and presenting the meeting. (Photo courtesy of Steve McCaw)

The short-term grants are just the initial phase of funding that is expected to total \$9 million over fiscal years 2016–2018.

Developing scaffolding for a new kind of infectious disease response

“We wanted to use this meeting as a working session,” Hughes said in his welcome remarks, “to help lay some groundwork for the [multifaceted] infectious disease response effort that we are undertaking jointly with NIOSH [National Institute for Occupational Safety and Health] and CDC [Centers for Disease Control and Prevention].”

As he explained, the initiative is a bold new step for WTP because it is more comprehensive than the immediate, single-disaster responses that were mounted following hurricanes Katrina and Sandy, the World Trade Center attack, and the Gulf oil spill.

According to NIEHS Division of Extramural Research and Training Director Gwen Collman, Ph.D., WTP can play a pivotal role in developing a new flexible response-training program. “It’s been a very interesting experience for NIEHS to get more involved in the infectious disease world,” she said, “and think about worker health and safety under new circumstances.”

The wider focus makes sense because, in the words of Kevin Yeskey, M.D., of the NIEHS [National Clearinghouse for Worker Safety and Health Training](#), “Ebola will come and go, but there are other things out there as well.”

Prevention as well as response

The broadest type of instruction funded by the program should raise awareness so that workers know when and where to seek expert help, without needlessly endangering their own lives and health. As grantee Mark Catlin, of the Service Employees International Union (SEIU), pointed out, workers need to understand what they do not have to do and how to avoid the reckless heroic response that may cause more harm than good.

The focus of the training, which is planned at sites across the U.S., will be necessarily broad to effectively train for emerging threats, explained grantee Janelle Rios, Ph.D., of the University of Texas at Houston. “We don’t know what’s next,” she said.

Building an infrastructure to respond to infectious disease

The first phase supports pilot programs by six organizations, to reach nearly 4,000 workers across the U.S. by July 31.

- International Chemical Workers Union Council (ICWUC) Center for Worker Health and Safety Education
- International Brotherhood of Teamsters
- Rutgers University School of Public Health
- SEIU Education and Support Fund
- United Steelworkers Union
- University of Texas Health Sciences Center at Houston

In addition to the best practices and training designs these programs will develop over the next two months, the grantees will be able to access resources developed by WTP, individual states, and federal partners. The federal agencies include the [CDC](#), [NIOSH](#), [Occupational Safety and Health Administration](#), and Office of the [Assistant Secretary for Preparedness and Response](#) in the U.S. Department of Health and Human Services.



“It’s not only frontline health workers that are in harm’s way [from Ebola and other infectious diseases],” Collman told the attendees. “There are lots of community support people in lots of the environments where people go when they’re sick.” (Photo courtesy of Steve McCaw)



Yeskey led a lively discussion about the draft “Training Competencies to Prepare Workers with Potential Exposure to Biological Hazards” that WTP Program Analyst Jim Remington and WTP contractor Nina Jaitly, M.D., developed for the meeting. (Photo courtesy of Steve McCaw)



SEIU lead researcher Catlin said his awareness training program will target allied health workers, janitors, airport workers, and others who were left out of earlier training for direct health care providers. (Photo courtesy of Steve McCaw)



John Morawetz, left, of ICWUC Center for Worker Health and Safety Education, and Darryl Alexander, of the American Federation of Teachers, underscored the importance of training with a broad scope to address the range of infectious diseases. “We don’t want this to sunset [because a single threat is past],” Alexander said. (Photo courtesy of Steve McCaw)



Rodrigo Toscano, of the United Steelworkers Union, described plans to conduct bilingual training for immigrant workers at medical centers in New York and California, saying that he expects literacy and translation to be the greatest challenges. (Photo courtesy of Steve McCaw)



Shawn Gibbs, Ph.D., left, of University of Nebraska Medical Center, and Rios are targeting first responders, public health officials, waste handlers, and hospital employees with awareness, operations, and community training. (Photo courtesy of Steve McCaw)



Sue Ann Sarpy, Ph.D., a consultant who specializes in training program evaluation, said the programs need to include outcome measures that demonstrate impact, “to show if we’ve moved the needle, and, if not, why not.” (Photo courtesy of Steve McCaw)

(Eddy Ball, Ph.D., is a contract writer with the NIEHS Office of Communications and Public Liaison.)

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Clinical Feature

NIEHS participates in first international myositis conference

By Robin Arnette

Researchers from around world gathered at the First International Conference on Myositis May 8-11 in Stockholm, Sweden. Scientists who study myositis, a rare autoimmune disease that causes muscle weakness, gathered to discuss the underlying causes and potential treatments for the disorder.

Lisa Rider, M.D., deputy chief of the NIEHS [Environmental Autoimmunity Group](#), was one of the 155 scientists and clinicians who attended the international assembly. As the first scientific conference dedicated entirely to myositis, the event drew participants from Europe, North America, Asia, and Australia.



Multidisciplinary event moves the field forward

“This conference was attended by many of the leading researchers in myositis, who for the first time, all sat together in the same room to learn about and discuss the latest scientific advances,” Rider said. “Myositis patients are cared for by a multidisciplinary team, so having a way for myositis specialists to share what they’ve found definitely furthers the field.”

Rider co-chaired a session on genes and the environment, and gave two separate oral presentations — one on the clinical and autoantibody phenotypes, or characteristics, of juvenile myositis, and a second on the development of new response criteria for adult and juvenile myositis.

Rider and her mentor, Frederick Miller, M.D., Ph.D., head of the NIEHS Environmental Autoimmunity Group, were both members of the scientific committee that organized the conference. Miller’s fellow committee members elected him as chair of the next International Conference on Myositis, to be held in the U.S. in 2017. Miller will take over for this year’s chair, Ingrid Lundberg, M.D., Ph.D., professor of rheumatology at the Karolinska Institutet in Stockholm.

Studying myositis here at home

Miller and Rider lead a research study in the U.S. to determine why American service members develop myositis at a rate that is double that of civilians.

The study, “[Environmental Risk Factors for Myositis in Military Personnel](#),” is recruiting participants (see [story](#)).



Several conference attendees took a quick break between sessions. From left, Lundberg; Paul Plotz, M.D., National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS); Rider; Andrew Mammen, M.D., Ph.D., NIAMS; Pari Basharat, M.D., London, Ontario, Canada; Michael Feely, Ph.D., University of Nebraska Medical Center; and Eleni Tiniakou, M.D., Johns Hopkins School of Medicine. (Photo courtesy of Kanneboyina Nagaraju, D.V.M., Ph.D., Children’s National Medical Center)

“I hope to build on the wonderful success of this meeting by inviting not only myositis experts, but also members of myositis patient advocacy groups, such as The Myositis Association and the Cure JM Foundation,” Miller said. “Researchers and patients will both benefit from the open exchange of information.”



Conference participants gathered for a group photo. (Photo courtesy of Ingrid Lundberg)

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Science Notebook

NTP completes chemical spill studies, finds water advisory level protective

By Robin Mackar

In less than a year, the National Toxicology Program (NTP) completed studies that may reassure West Virginia residents impacted by a chemical spill that there is very little reason for concern about long-term health effects.

[Scott Auerbach, Ph.D.](#), one of the lead NTP scientists working on this effort, presented the study findings at the June 16 NTP Board of Scientific Counselors meeting.

“All together, the NTP findings support the adequacy of the drinking water advisory levels established at the time of the spill,” Auerbach said at the meeting. A 1 part per million (ppm) drinking water advisory for 4-methylcyclohexanemethanol (MCHM), the main chemical spilled, was established by the Centers for Disease Control and Prevention (CDC) and West Virginia health officials in early 2014.



Auerbach oversaw the work of a team of scientists and administrators from across the institute to tackle the difficult project of conducting the broad battery of tests. (Photo courtesy of Steve McCaw)

NTP designs and implements a comprehensive research plan

Because there were few toxicology studies available at the time of the spill, the NTP received a [nomination](#) from CDC to develop a research plan that would provide meaningful information to public health decision-makers within a year.

The NTP designed and implemented short-term toxicity studies using a variety of toxicology models in assays that represented a wide spectrum of biology.

The studies included predictions of health effects based on computer models of chemical structure and toxicity; studies of gene mutations in bacteria; growth, development, and behavior in roundworms; developmental studies in zebrafish embryos; toxicity to human cells in culture; and toxicogenomic and prenatal toxicity studies in rodents.

NTP conclusions

The NTP concluded that the combined study findings support the adequacy of the drinking water advisory levels established at the time of the spill. Studies, in which pregnant rats were given MCHM, found that pups had lower fetal weights, but only at high doses of MCHM. The prenatal developmental toxicity study followed a standard protocol designed to test whether chemicals have the ability to affect normal fetal development in a pregnant rat.

Although of little concern, this result identified a vulnerable life stage in rodents, and suggested an opportunity to evaluate a potential health effect in the affected communities. No significant health effects were found for the other spilled chemicals. The NTP also did not find genotoxicity in any of its studies, reducing the concerns related to long-term effects such as cancer.

Sharing study results

The NTP has been working closely since the spill with the [West Virginia Department of Health and Human Resources](#) and other state, local, and federal entities to share the study results and communicate these findings to local residents. The NTP also has been continually updating the study results on [dedicated web pages](#) since the studies began.

“We hope these studies bring some reassurance to the people of West Virginia,” said John Bucher, Ph.D., associate director of NTP. “We used the best tools that toxicology has to offer to look at these spilled chemicals, and we found very little reason for concern.”

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

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Walker delivers one-two punch for chemotherapy and antibiotics

By Geoff Feld

When DNA becomes damaged, cells use specialized machinery, known as translesion synthesis (TLS) polymerases, in the DNA replication process. Graham Walker, Ph.D., presented a historical perspective on these specialized molecules at the May 28 Keystone Science Lecture Seminar Series. [Walker](#), a professor at Massachusetts Institute of Technology (MIT) and a Howard Hughes Medical Institute (HHMI) Professor, also discussed his group’s recent advances, which have implications for both human cancer treatment and bacterial antibiotics.

Walker credited geneticist Evelyn Witkin, Ph.D., for laying the foundation for his research. Her work on radiation-resistant bacteria in the 1960s and 1970s led to the discovery of a response to DNA damage known as the SOS response, which includes an error-prone DNA repair pathway.

As a postdoctoral fellow, and later in his own lab, Walker extended these discoveries to bacteria and to higher life forms, including humans. His work contributed to the characterization of the error-prone TLS polymerases known as Rev1 and DNA pol zeta (Rev3-Rev7). Walker dedicated his talk to the 94-year-old Witkin, with whom he had dinner just last year.

A passion for teaching

In 2002, Walker was named one of 20 original participants in the society of [HHMI Professors](#).

Since his appointment, the society has supported the Education Group in the MIT Department of Biology, which provides innovative tools for the interactive teaching of biological concepts.

The Education Group has made several software packages freely available, including [StarGenetics](#), a genetic cross simulator, and [StarBiochem](#), a molecular graphics viewer.

Knocking down errors improves cancer treatment

Walker said that all too often, animal models and clinical trials of cancer therapeutics follow an unfortunate sequence, with an early apparent success followed by reappearance of the tumor. These long-term failures intrigued Walker, and he hypothesized that the problem lay in TLS polymerases, whose errors may induce mutations.

“Cancer is a disease of mutations,” he explained. “If you look at the genomes of tumors from lung cancers or melanomas, they’re just loaded with mutations whose signatures look like they come from the action of these DNA polymerases.” The polymerases, which are enzymes, introduce errors at chemotherapy-derived DNA damage sites, he said, providing tumors with the mutational means to develop resistance.

In the last five years, Walker’s lab has published a number of findings that support this hypothesis. In mice models, they found that decreasing the level of expression of Rev1 (Xie K, et al., 2010) or Rev3 (Doles J, et al., 2010) in the tumors improved the outcomes of two DNA-damaging chemotherapeutic drugs, cyclophosphamide and cisplatin.

Walker, an avid collaborator, has reached out to numerous labs to further develop chemotherapeutic approaches. For example, he worked with [Omid Farokhzad, M.D.](#), of Harvard Medical School, and his nanoparticle platform, to co-deliver small interfering RNA (siRNA) molecules together with a cisplatin prodrug, which significantly enhanced the results (Xu X, et al., 2013).

Avoiding an impending crisis

Walker alluded to the “big crisis coming up” for antibiotics, because resistance is increasing while approvals of new antibacterial drug applications have sharply declined. According to Walker, his research on bacterial TLS enzymes has led to new insights into how antibiotics kill cells.

In addition to acting on specific molecular targets, antibiotics may lead to metabolic stress and oxidation of important molecules in bacteria. Sam Wilson, Ph.D., chief of the NIEHS [DNA Repair and Nucleic Acid Enzymology Group](#), pioneered the study of 8-oxo-dGTP, which is the oxidized product of the deoxynucleotide guanosine triphosphate, which is incorporated into DNA.

Building upon Wilson’s work and working with NIEHS funding, Walker’s laboratory has extensively studied a bacterial TLS polymerase known as DinB, which preferentially incorporates 8-oxo-GTP into the genome, resulting in DNA damage.



Walker discussed a crystal structure of Rev complexes, obtained in collaboration with Pei Zhou, Ph.D., of Duke Medical School (see Wojtaszek J et al., 2012). He described the interaction between Rev7 and the Rev3 peptide as a seat belt, demonstrating for the audience. (Photo courtesy of Steve McCaw)



Dan Shaughnessy, Ph.D., of the NIEHS Exposure, Response, and Technology Branch, hosted Walker’s talk and moderated the discussion session afterwards. Shaughnessy oversees grants related to DNA repair and mutagenesis, as well as other areas. (Photo courtesy of Steve McCaw)

“We then fiddled with the DNA polymerase composition to make the cells less able to put in 8-oxo-dG and we saw protective effect against bactericidal antibiotics,” explained Walker (Foti JJ, et al., 2012).

Citations:

Doles J, Oliver TG, Cameron ER, Hsu G, Jacks T, Walker GC, Hemann MT. 2010. Suppression of Rev3, the catalytic subunit of Pol{zeta}, sensitizes drug-resistant lung tumors to chemotherapy. Proc Natl Acad Sci U S A 107(48):20786-20791.

Foti JJ, Devadoss B, Winkler JA, Collins JJ, Walker GC. 2012. Oxidation of the guanine nucleotide pool underlies cell death by bactericidal antibiotics. Science 336(6079):315-319.

Wojtaszek J, Lee C-J, D’Souza S, Minesinger B, Kim H, D’Andrea AD, Walker GC, Zhou P. 2012. Structural basis of Rev1-mediated assembly of a quaternary vertebrate translesion polymerase complex consisting of Rev1, heterodimeric polymerase (Pol) zeta, and Pol kappa. J Biol Chem. 287(40):33836-33846.

Xie K, Doles J, Hemann MT, Walker GC. 2010. Error-prone translesion synthesis mediates acquired chemoresistance. Proc Natl Acad Sci U S A 107(48):20792-20797.

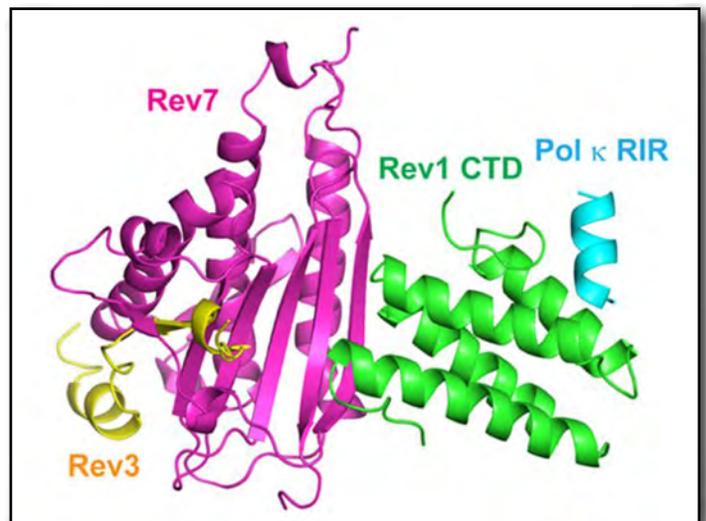
Xu X, Xie K, Zhang XQ, Pridgen EM, Park GY, Cui DS, Shi J, Wu J, Kantoff PW, Lippard SJ, Langer R, Walker GC, Farokhzad OC. 2013. Enhancing tumor cell response to chemotherapy through nanoparticle-mediated codelivery of siRNA and cisplatin prodrug. Proc Natl Acad Sci U S A 110(46):18638-18643.

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

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Bill Copeland, Ph.D., left, who leads the Genome Integrity and Structural Biology Laboratory, and Dmitri Gordenin, Ph.D., chief of the Mechanism of Genome Dynamics Group, were among the audience that came from all divisions of the institute. (Photo courtesy of Steve McCaw)



Walker presented the central findings from the Wojtaszek J et al. paper, revealing the structure of the Rev1 C-terminal domain (CTD)-Rev3/7-Pol kappa Rev1 interacting region (RIR) complex. (Source: Wojtaszek J, et al., 2012)

Is cancer mainly bad luck? NIEHS scientists respond

By Kelly Lenox

A study published January 2 in the journal *Science* attracted attention in the scientific and popular press alike for its conclusions, which were often summarized as “cancer is just bad luck.” The study, “[Cancer etiology. Variation in cancer risk among tissues can be explained by the number of stem cell divisions](#),” was conducted by [Cristian Tomasetti, Ph.D.](#), and [Bert Vogelstein, M.D.](#), both with the Johns Hopkins Kimmel Cancer Center.

Two NIEHS scientists, Clarice Weinberg, Ph.D., and Dmitri Zaykin, Ph.D., published a [commentary](#) in the *Journal of the National Cancer Institute*, providing another perspective on the original study (see [summary](#)). “While bad luck may play an important role in carcinogenesis,” they wrote, “the data do not compel that conclusion.”

Taking a closer look

Tomasetti and Vogelstein compared average lifetime incidence rates of 31 site-specific types of cancer with the number of stem cell divisions for the associated tissues, and after plotting logarithms, they found an association between stem cell division and cancer rates. “These results suggest that only a third of the variation in cancer risk among tissues is attributable to environmental factors or inherited predispositions,” they wrote. “The majority is due to ‘bad luck,’ that is, random mutations in normal, noncancerous stem cells.”

Weinberg, head of the NIEHS [Biostatistics and Computational Biology Branch](#), and Zaykin, a lead researcher in that branch, took a closer look at the data and raised three statistical concerns.

Correlation is not causation

First, the NIEHS scientists discussed the comparison of lifetime risk of certain site-specific cancers with total stem cell divisions in the associated tissues. Statisticians use a value called R squared to represent the correlation between two different measured variables. The closer the value is to 1, the more closely correlated the two variables are.

Tomasetti and Vogelstein reported the R squared value for their data as 0.65, concluding that 65 percent, or about two-thirds, of the differences in cancer risk among different tissues can be explained by the total number of stem cell divisions in those tissues.



“There is value in pointing out this relationship,” Weinberg said, “in that the errors due to replication are probably causatively important. [But] they went too far when they implied that inherited genetics and environmental factors could only explain about one-third of cancer.”
(Photo courtesy of Steve McCaw)

PubMed Commons provides forum for scientific discussion

The National Library of Medicine of the National Institutes of Health enhanced the popular PubMed site in December 2013 with the launch of PubMed Commons as a forum for scientific discussion.

Any author in the PubMed database may join the commons and comment on scientific publications. Plus, all viewers of a PubMed abstract can scroll down and freely read commentary posted by scientists. The [Tomasetti, Vogelstein article](#) has attracted 12 commenters to date, each of whom addresses one or more aspects of the piece in detail.

More information on the forum is available on the [PubMed Commons Blog](#) and the [PubMed Commons home page](#).

And this is where terminology becomes important. “Explaining’ is statistical jargon that has little to do with causation — it has to do with the relationship between X and Y,” Weinberg said. “You can’t conclude from an R squared value how much of that causal relationship is actually due to the variable that X represents.”

Aggregate risk and multiple causes

A second concern Weinberg and Zaykin raised was the use of aggregated lifetime risk data, a point raised by other commenters. “The R squared from an analysis of cancer types based on aggregated risk for each type obscures the contributions of individual risk factors to each cancer type,” they wrote.

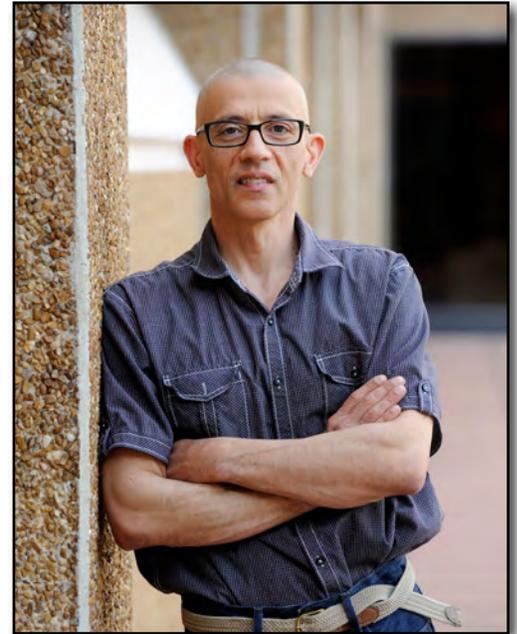
Finally, they addressed the researchers’ approach of partitioning different causes into fractions that add up to 1. Referring to phenylketonuria, an inherited condition in which the body cannot properly metabolize phenylalanine, they wrote, “The fraction attributable to genetics is 1.0, while the fraction attributable to environment is also 1.0, because the outcome requires both a dysfunctional metabolic gene and an environmental exposure [dietary phenylalanine].”

“Weinberg and Zaykin make important points,” said NIEHS Scientific Director Darryl Zeldin, M.D. “The claim that two-thirds of the cancers studied are caused by bad luck could lead to an overemphasis on development of treatments, at the expense of crucial research into prevention and the role that environmental and genetic factors play in the origins of cancer.”

Other commentary, other forums

Weinberg and Zaykin were not the only NIEHS scientists to enter the debate. NIEHS biostatistician [Shyamal Peddada, Ph.D.](#), posted an [online comment](#) on the Science paper, suggesting that the authors’ mathematical approach, which used log-transformed data, led to a faulty conclusion. “[It] is not supported by the raw data given in their Table S1,” Peddada wrote. “A correlation analysis of the raw data reveals a weak correlation, with only 28 percent of the variability in lifetime risk of developing cancer explained by the total number of stem cell divisions.”

Besides commentary on the Science website, the paper was vigorously discussed in PubMedCommons (see [sidebar](#)). The public debate underscores the important contribution that open dialogue and data access can make to ensuring that new scientific findings are properly interpreted, so they can be confirmed and appropriately followed up in future studies.



Zaykin elaborated on his concern with aggregating the lifetime risk data. “If you looked at individuals, you would have a more spread out cloud [of dots on the graph], because each individual has their own set of potential causes,” he said. “The resulting correlation could drop substantially. All we can say is that bad luck is in that mix.” (Photo courtesy of Steve McCaw)



Supporting his online call for caution when interpreting correlation coefficients, Peddada wrote, “Further probing of the raw data reveals that [three of the cancers studied,] colorectal, Lynch colorectal, and FAP colorectal tissues, have the same number of stem cell divisions (1.17×10^{E12}) and yet have widely different lifetime risk estimates (0.05, 0.50, and 1.00, respectively), covering almost the entire range of possible values for risk (i.e., 0 to 1).” (Photo courtesy of Steve McCaw)

Citations:

[Tomasetti C, Vogelstein B](#). 2015. Cancer etiology. Variation in cancer risk among tissues can be explained by the number of stem cell divisions. *Science* 347(6217):78-81.

[Weinberg CR, Zaykin D](#). 2015. Is bad luck the main cause of cancer? *J Natl Cancer Inst.* 107(7):djv125.

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New data tools top the agenda at NTP board meeting

By Ernie Hood

New and maturing tools to aid the process of systematic review and overall NTP research efforts took center stage at the June 16 [meeting](#) of the National Toxicology Program (NTP) Board of Scientific Counselors (BSC).

Representatives of the NTP Office of Health Assessment and Translation (OHAT) briefed the board on several quickly developing innovations. The board also approved two contract concepts and heard updates on topics, such as NTP's analysis of the chemicals in the 2014 Elk River chemical spill (see [story](#)) and an NTP research project to update the levels of concern categories used in NTP conclusions about the hazard identification of environmental exposures.

Hopeful signs on the budget

Later in the morning, after NIEHS and NTP Director Linda Birnbaum, Ph.D., reported on recent and upcoming developments at NTP, she shared an up-to-the-minute news flash from Capitol Hill. The full House Appropriations Committee had just released its fiscal year 2016 Labor, Health, and Human Services [funding bill](#), which includes funding recommendations for the National Institutes of Health (NIH), the parent agency of NIEHS.

In his report, NTP Associate Director John Bucher, Ph.D., announced that Kristina Thayer, Ph.D., was named Deputy Director for Analysis in the Division of the NTP (DNTP). In her new position, Thayer will oversee both OHAT and the Office of the Report on Carcinogens, and she will be responsible for continuing to advance the use of systematic review in environmental health sciences.

Expanding the toolkit

Thayer kicked off a session devoted to briefing the board on new software advances to make the process of conducting a systematic review more efficient, focusing on tools for text mining and machine learning, structured data extraction, and data display.



Bucher announced that DNTP was awarded some of the funds redirected after cancellation of the National Children's Study (NCS) by NIH in December. Remaining true to the original intent of the study, DNTP will use the funds to expand the Tox21 program to encompass a Developmental Toxicity Program. (Photo courtesy of Steve McCaw)

OHAT has been working extensively to implement systematic review methods, including release of a [handbook on conducting systematic reviews](#) in January 2015. “Parallel to adopting principles of systematic review, we’ve made a pretty large investment in tool development,” said Thayer. “These tools have really matured in the past year, to the point now that they can regularly be seen as part of OHAT projects.”

One of the new tools, called **SWIFT** (Sciome Workbench for Interactive Computer-Facilitated Text Mining), will be released for use later this year and will be freely available. Contractor Ruchir Shah, Ph.D., from Sciome LLC, described the tool as a user-friendly workbench to explore, categorize, search, and perform topic discovery. SWIFT also provides methods to prioritize documents to facilitate screening, with the goal of making the screening process more efficient.

“We started taking concepts from the fields of text mining, information retrieval, and machine learning to statistically analyze large collections of documents,” Shah explained. Among other applications, SWIFT will be used to help generate a new form of OHAT document called a scoping report, which provides an overall sense of the literature on a specific topic.

OHAT researcher Katherine Pelch, Ph.D., told the board about the first scoping report using the SWIFT text-mining tool to effectively winnow down an enormous number of potential references for a systematic review, in this case, on environmental influences on the epigenome.



Thayer enjoyed one of the lighter moments in a detailed discussion of new data analysis tools that promise to advance systematic review. (Photo courtesy of Steve McCaw)



Late spring in North Carolina presented the perfect opportunity for a group photo of the BSC, along with Birnbaum and Bucher. Shown seated, from left, are Sonya Sobrian, Ph.D.; Lisa Peterson, Ph.D.; Birnbaum; and Iris Udasin, M.D. Standing, from left, are Dale Hattis, Ph.D.; Bucher; Paul Howard, Ph.D.; George Corcoran, Ph.D.; David Dorman, D.V.M.; and Kass. (Photo courtesy of Steve McCaw)



Ad hoc BSC member Daniel Kass, deputy commissioner of the New York City Department of Health and Mental Hygiene, paid close attention at his first meeting and contributed several incisive comments. (Photo courtesy of Steve McCaw)

Data scientist Andy Shapiro, from the NTP Program Operations Branch, presented another tool being developed called **HAWC** (Health Assessment Workspace Collaboration), a web-based content management system for human health assessments, and its recent application to OHAT assessments.

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



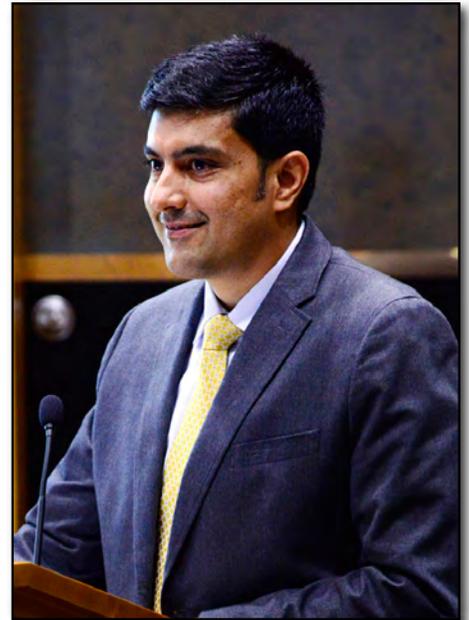
Dorman, of North Carolina State University, brought a touch of color to the proceedings with his Wolfpack red shirt. (Photo courtesy of Steve McCaw)



A moment of humor during the meeting was enjoyed by, from left, Birnbaum, Bucher, Board Chair Lisa Peterson, Ph.D., and DNTP Deputy Director for Science Nigel Walker, Ph.D. (Photo courtesy of Steve McCaw)



Comments from board member Robert Chapin, Ph.D., from Pfizer, are always good-natured yet scientifically penetrating. (Photo courtesy of Steve McCaw)



Shah noted that SWIFT is still undergoing development and expansion of its capabilities, including eventual integration with HAWC. (Photo courtesy of Steve McCaw)



The dialogues during breaks are often as important as the proceedings themselves. From left, Hattis, of Clark University, confers with Stephanie Holmgren from the NIEHS Office of Scientific Information, and Corcoran, of Wayne State University. Holmgren made a presentation to the board on how to systematically search the literature, a key step in the systematic review process. (Photo courtesy of Steve McCaw)



Shapiro was particularly proud to display the new HAWC logo. The project is an expansion of his master's thesis at the University of North Carolina at Chapel Hill, and the software is currently being used by the World Health Organization International Agency for Research on Cancer monographs program, as well as by OHAT. (Photo courtesy of Steve McCaw)

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Metabolomics as a tool for exposure science

By Kelly Lenox

Experts in exposure science joined researchers in metabolomics at a Washington D.C. workshop held by the National Research Council (NRC), planned in conjunction with NIEHS. The May 28-29 event, “Metabolomics as a Tool for Characterizing the Exposome,” explored contributions that the science of metabolomics, which is the study of the chemical fingerprints that cellular processes leave behind, can make to the study of human exposures over the lifetime, which is known as the exposome.

Although significant challenges remain (see [sidebar](#)), the workshop demonstrated that metabolomics is a promising addition to exposure data obtained from monitors and sensors. “I think there are great possibilities for discovery,” said workshop moderator Chirag Patel, Ph.D., who is from Harvard University and serves on the NRC [Standing Committee on Use of Emerging Science for Environmental Health Decisions](#), which sponsored the workshop.

Exposome studies provide insights into disease

Patel began by explaining that diseases generally result from interactions between genes and exposures. Genome-wide association studies help scientists understand genetic contributions, but exposure science is not as far along. “We lack [adequate] methods to ascertain and assess exposures,” Patel said, summarizing a January exposome workshop at NIEHS (see [story](#)), which led to this event.

David Balshaw, Ph.D., chief of the NIEHS Exposure, Response, and Technology Branch, provided the context for NIEHS. “The exposome features prominently in two of our [strategic plan](#) goals,” he said. Those goals include transforming exposure science, by helping to define the concept of the exposome and how it might be applied in research, as well as chemical mixtures research, which involves the study of interactions between environmental factors.

[Stephen Rappaport, Ph.D.](#), from the University of California, Berkeley, pointed out that overall health may be affected by exposures, which can be seen as causal pathways, and the body’s responses to exposure, or reactive pathways. Rappaport explained that studying the metabolome through untargeted exposome-wide association studies may help identify disease biomarkers.



Patel, shown above at the January NIEHS workshop, when he chaired the workgroup on data science, is an assistant professor at the Harvard Center for Biomedical Informatics. (Photo courtesy of Steve McCaw)

Challenges of metabolomics studies

Discussions between panelists and the audience made it clear that each aspect of mining the metabolome for exposure information is fraught with its own set of challenges.

For example, factors important in sample collection include the timing of collection with respect to exposure, one-time versus long-term collection, and preserving the right metadata, such as the known disease states of participants. Furthermore, both host genetics and bacterial genetics may drive effects in the body, so information on the microbiome is needed. Reproducibility was also discussed at length.

[David Wishart, Ph.D.](#), from the University of Alberta, described several metabolomics databases, including the [Human Metabolome Database](#), which contains free information on more than 40,000 metabolites. He emphasized that study of metabolites can be fast, cheap, and informative, and it is rapidly evolving. “It’s in the early days still,” he said, “so these are exciting times.”



Linked Audio: (Launches in new window)
[Listen to Wishart discuss human metabolomics research at the University of Alberta, and a study that revealed more than 3,000 compounds in human urine, in this Radio Canada International podcast. \(7:12\)](#)

Download Media Player:  Quicktime 

Many questions remain

The questions guiding the final panel discussion underscored the emerging nature of the topic. They included:

- Can the metabolome help us to understand adverse outcome pathways, based on changes to the metabolome associated with long-term low-level exposures?
- Can the metabolome help us identify susceptible individuals or populations by flagging pre-existing disease or concurrent exposures, which affect response?
- How can metabolomics data be incorporated into epidemiological studies?
- How will the answers to these questions help us to bring the exposome concept into the risk assessment process?
- What are the implications of metabolomics information for the public understanding of their risk?

The way forward

Rappaport addressed the infrastructure necessary to moving forward. “It’s a big enough ... project that we need to get cooperation from government, academia, and industry, especially the industries that are involved with technology development,” he said.

William Farland, Ph.D., from Colorado State University and chair of the NRC standing committee, summed up the workshop with a look ahead. “The final discussion, about the chemists and toxicologists and epidemiologists getting together, [points out] that this is a big data problem that’s going to require multidisciplinary types of approaches.”

NRC prepared a summary report and posted the agenda, speaker biographies and slides, and a video playlist on its [webpage for the workshop](#).

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Farland articulated the hopes of many of the experts present. “We are looking to do science that can enable action,” he said. (Photo courtesy of NRC)



Panelist Susan Sumner, Ph.D., directs the National Institutes of Health Eastern Regional Comprehensive Metabolomics Research Center at RTI International, in Research Triangle Park, North Carolina. (Photo courtesy of NRC)



Elaine Cohen Hubal, Ph.D. from the U.S. Environmental Protection Agency, described the agency’s Chemical Safety for Sustainability research program, which provides tools to support production and use of safer chemicals. Prediction of exposure levels and effects are integral to that effort. (Photo courtesy of NRC)



“The greatest utility [of the exposome] will be in the area of disease etiology, or finding causes of disease,” said Rappaport, who is a lead researcher at the Berkeley Center for Exposure Biology. (Photo courtesy of NRC)

NTP toxicologist Nigel Walker, Ph.D., earns prestigious award

By Danica Andrews

National Toxicology Program (NTP) Deputy Division Director for Science Nigel Walker, Ph.D., was honored June 4 with the 2015 Herbert E. Stokinger Award from the [American Conference of Governmental Industrial Hygienists](#) (ACGIH). Walker received this award during the American Industrial Hygiene Conference and Exposition in Salt Lake City, for his work on the toxicology and carcinogenicity of compounds associated with occupational and environmental exposures.

The [Stoking Award](#) recognizes individuals whose leadership and dedication have provided significant advancement to the fields of environmental toxicology and industrial toxicology. “I was not only honored and surprised, but also pretty humbled,” Walker said when he learned about the award. “One of my goals as a scientist in the National Toxicology Program is the development of sound science that people can trust when making decisions [regarding] potentially harmful substances in the environment and the workplace.”

Sharing the credit

“To receive this award is a significant accomplishment, and Nigel is more than deserving of this honor,” said John Bucher, Ph.D., director of the NTP division at NIEHS. “He joins a list of awardees that reads like a Who’s Who of toxicology and industrial health.”

Walker promptly gave credit to fellow NTP staff. “At NTP we [conduct science] in a real team-based environment,” he said. “So while as a member of NTP leadership I appear front and center on many scientific initiatives, I stand on the shoulders of all the NTP staff that support the projects that I have been involved in.” Walker said the award is a testament to the strength of the environmental toxicology work done by NTP.

Along with other NTP staff, Walker has been involved with research on the health effects of the [Elk River chemical spill](#) in West Virginia. “The way NTP responded to the Elk River Spill captures how NTP is always adapting to the changing scientific and societal environment,” he said. “And [we] use team science to effectively address issues with the tools of modern toxicology, to provide real solutions for problems that people come to us with.”

Walker, who was born in England, received his B.Sc. in biochemistry from the University of Bath and his Ph.D. in biochemistry from the University of Liverpool. He did postdoctoral research at both Johns Hopkins School of Hygiene and Public Health and NIEHS, before joining NTP. Walker jokes that he has now lived in North Carolina longer than he lived in England. He became a U.S. citizen in 2002.

(Danica Andrews is a program specialist in NTP.)

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Walker, left, received the award from J. Torey Nalbone, Ph.D., chair of the ACGIH Board of Directors. (Photo courtesy of the American Industrial Hygiene Association)

Assessing the potential health hazards of nanoscale materials

Walker delivered the Herbert Stockinger Award talk at the ACGIH conference June 4, titled “A 21st century Paradigm for Evaluating the Health Hazards of Agents in the Workplace: The Challenge of Nanoscale Materials.” He discussed the challenges that nanomaterials pose for traditional toxicity testing methods.

Nanomaterials are substances that are smaller than 100 nanometers in at least one dimension, and they can possess a wide variety of optical, magnetic, and electrical properties. Walker pointed out that these properties can result in unpredictable biological interactions that are difficult to study. He further stated that new high-throughput toxicity testing methods are being developed to bring greater precision to the understanding of the human health effects of these quickly evolving materials.

Exposure to low levels of chemical mixtures linked with cancer

By Sara Mishamandani

Chemicals can sometimes act together to cause cancer, even when low-level exposures to the individual chemicals might not be cancer-causing, or carcinogenic. This important finding emerged from an international task force of more than 170 cancer scientists, known as the Halifax Project, who collaboratively assessed the carcinogenic potential of low-dose exposures to chemical mixtures in the environment.

The [Halifax Project](#) task force published a [paper](#) in a [special issue](#) of the journal *Carcinogenesis* explaining their review of the key biological pathways and mechanisms related to the formation of cancer. “The Halifax Project was about getting cancer biologists to talk about the specific hallmarks of cancer that they research and the environmental exposures that contribute to those hallmarks,” said Danielle Carlin, Ph.D., NIEHS Superfund Research Program (SRP) health scientist administrator. Carlin was part of the task force and a co-author of the review paper.

“The researchers focused on chemicals that don’t get a lot of attention in cancer research because we don’t normally consider them carcinogens by themselves,” she said. “However, mixtures of these chemicals may contribute to cancer.”



Carlin is one of the leads on mixtures research at NIEHS, which focuses on better understanding how combined environmental exposures affect disease progression. (Photo courtesy of Steve McCaw)

NIEHS-funded workshop moves collaboration forward

The review stemmed from a Halifax Project [workshop](#) August 8-9, 2013 in Nova Scotia, Canada. “SRP is interested in the [NIEHS Strategic Plan](#) goal of understanding how combined environmental exposures affect disease pathogenesis,” Carlin said. “This meeting was funded by SRP to foster collaboration and work toward a better understanding of how the joint action of multiple chemical exposures may cause cancer.”

Before the meeting, eleven teams of experts were formed to focus on specific mechanistic contributors, or hallmarks, to cancer. Each team identified environmental exposures known to disrupt their particular hallmark. After the meeting, each group prepared a paper on their findings, which were published in a special issue of *Carcinogenesis*. The collection addressed hallmarks such as tissue invasion and metastasis, evading growth suppression, the tumor microenvironment, and genome instability.

Upcoming workshop – Statistical Approaches for Assessing Health Effects of Environmental Chemical Mixtures in Epidemiology Studies

NIEHS will host a two-day workshop July 13-14 on the development of statistical approaches and use of available statistical methods to analyze combined exposure data from epidemiological studies, a theme that has emerged as a key challenge in environmental chemical mixtures research.

The workshop will bring together experts in the fields of epidemiology and biostatistics to identify, develop, refine, and disseminate methods for quantifying the health effects of environmental chemical mixtures. It will be held in the main building at NIEHS. For more information or to register, visit the [meeting website](#). Registration closes July 2.

For the recently published article, the expert teams selected 85 chemicals to which the population is routinely exposed. The authors reported that 50 of them may disrupt cancer-related biological mechanisms at low doses.

Reviewing the challenges ahead

“We are definitely concerned that we are now starting to see evidence of a wide range of low-dose effects that are directly related to carcinogenesis, exerted by chemicals that are unavoidable in the environment,” said lead author [William Goodson III, M.D.](#), senior scientist at the California Pacific Medical Center in San Francisco.

“This is an area that merits considerable attention, and where interdisciplinary and international collaboration is needed,” said contributing author [David Carpenter, Ph.D.](#), director of the Institute for Health and the Environment at the University of Albany in New York. “Although we know a lot about the individual effects of chemicals, we know very little about the combined and additive effects of the many chemicals that we encounter every day in the air, in our water, and in our food.”

In addition to participating in the working groups during the meeting, Carlin gave a presentation on NIEHS priorities and described how NIEHS-funded researchers are working to unravel the health effects of environmental mixtures. Rick Woychik, Ph.D., NIEHS deputy director, gave the keynote on strategic directions in environmental health, and National Toxicology Program toxicologist Cynthia Rider, Ph.D., gave a presentation addressing experimental designs and approaches to studying mixtures, and the importance of studying environmental chemicals as contributors to the onset of cancer.

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



Participants from around the world used the Halifax Project workshop to collaborate and generate recommendations for advancing mixtures research related to cancer. (Photo courtesy of Danielle Carlin)

Citation: Goodson WH 3rd, Lowe L, Carpenter DO, Gilbertson M, Manaf Ali A, Lopez de Cerain Salsamendi A, Lasfar A, Carnero A, Azqueta A, Amedei A, Charles AK, Collins AR, Ward A, Salzberg AC, Colacci A, Olsen AK, Berg A, Barclay BJ, Zhou BP, Blanco-Aparicio C, Baglolle CJ, Dong C, Mondello C, Hsu CW, Naus CC, Yedjou C, Curran CS, Laird DW, Koch DC, Carlin DJ, Felsher DW, Roy D, Brown DG, Ratovitski E, Ryan EP, Corsini E, Rojas E, Moon EY, Laconi E, Marongiu F, Al-Mulla F, Chiaradonna F, Darroudi F, Martin FL, Van Schooten FJ, Goldberg GS, Wagemaker G, Nangami G, Calaf GM, Williams G, Wolf GT, Koppen G, Brunborg G, Kim Lyerly H, Krishnan H, Ab Hamid H, Yasaei H, Sone H, Kondoh H, Salem HK, Hsu HY, Park HH, Koturbash I, Miousse IR, Scovassi AI, Klaunig JE, Vondráček J, Raju J, Roman J, Wise JP Sr, Whitfield JR, Woodrick J, Christopher JA, Ochieng J, Martinez-Leal JF, Weisz J, Kravchenko J, Sun J, Prudhomme KR, Narayanan KB, Cohen-Solal KA, Moorwood K, Gonzalez L, Soucek L, Jian L, D'Abronzio LS, Lin LT, Li L, Gulliver L, McCawley LJ, Memeo L, Vermeulen L, Leyns L, Zhang L, Valverde M, Khatami M, Romano MF, Chapellier M, Williams MA, Wade M, Manjili MH, Lleonart M, Xia M, Gonzalez MJ, Karamouzis MV, Kirsch-Volders M, Vaccari M, Kuemmerle NB, Singh N, Cruickshanks N, Kleinstreuer N, van Larebeke N, Ahmed N, Ogunkua O, Krishnakumar PK, Vadgama P, Marignani PA, Ghosh PM, Ostrosky-Wegman P, Thompson P, Dent P, Heneberg P, Darbre P, Sing Leung P, Nangia-Makker P, Cheng QS, Robey RB, Al-Temaimi R, Roy R, Andrade-Vieira R, Sinha RK, Mehta R, Vento R, Di Fiore R, Ponce-Cusi R, Dornetshuber-Fleiss R, Nahta R, Castellino RC, Palorini R, Abd Hamid R, Langie SA, Eltom S, Brooks SA, Ryeom S, Wise SS, Bay SN, Harris SA, Papagerakis S, Romano S, Pavanello S, Eriksson S, Forte S, Casey SC, Luanpitpong S, Lee TJ, Otsuki T, Chen T, Massfelder T, Sanderson T, Guarnieri T, Hultman T, Dormoy V, Otero-Marah V, Sabbisetti V, Maguer-Satta V, Rathmell WK, Engström W, Decker WK, Bisson WH, Rojanasakul Y, Luqmani Y, Chen Z, Hu Z. 2015. Assessing the carcinogenic potential of low-dose exposures to chemical mixtures in the environment: the challenge ahead. *Carcinogenesis* 36(Suppl 1):S254–S296.

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This month in EHP

The July issue of Environmental Health Perspectives (EHP) examines the difficulties of developing safer food packaging to reduce chemical leaching.



<http://twitter.com/ehponline>

Focus feature:

A Hard Nut to Crack: Reducing Chemical Migration in Food-Contact Materials

Although food packaging serves important safety functions, these painstakingly engineered containers can also leach chemicals and other contaminants into the food and drink they protect. Researchers and food producers are searching for ways to stem this chemical migration, but solutions are proving elusive.

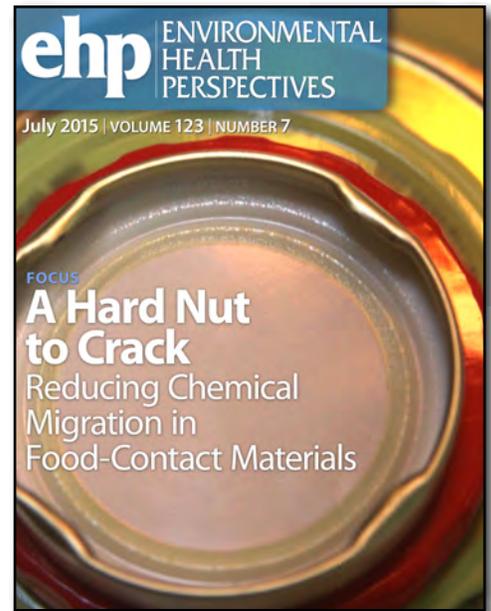
Spheres of influence feature:

A Second Life for Scraps: Making Biogas From Food Waste

Decomposing food waste is a rich source of methane gas. In landfills, this presents a problem because escaping methane contributes to the greenhouse effect. Now, communities and food retailers are beginning to divert food waste to anaerobic digesters, capturing the resulting gas for use as fuel.

Research summaries featured this month include:

- **Increased Minimum Mortality Temperature in France: Data Suggest Humans Are Adapting to Climate Change** — A new study based on 42 years of climatic and mortality data shows that the minimum mortality temperature in France has increased over time, suggesting some measure of adaptation to warming during that period.
- **New Risk Factor for Sudden Infant Death Syndrome (SIDS)? Peaks in Cot Deaths Associated with Heat Waves** — A new study of SIDS deaths suggests that hotter outdoor temperatures also may be a risk factor.
- **What's Normal for Fracking? Estimating Total Radioactivity of Produced Fluids** — Researchers estimate total reactivity for a mixture of isotopes present in liquid fracking waste from Marcellus Shale.
- **Persistent organic pollutants and Gut Microbiota: Dietary Exposure Alters Ratio of Bacterial Species** — Researchers report that 2,3,7,8-tetrachlorodibenzofuran (TCDF) alters the mouse gut microbiome in ways that may contribute to obesity and other metabolic diseases.



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Extramural papers of the month

By [Nancy Lamontagne](#)

- [Monitoring gene mutation using low volume blood samples](#)
- [3-D cell culture provides model to study toxicant effects on endocervix](#)
- [Faster assessment of carcinogenic potential for PAH mixtures](#)
- [Th17 cells convert into regulatory T cells during immune response](#)

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

Monitoring gene mutation using low volume blood samples

An NIEHS Small Business Innovative Research grantee and colleagues developed a simple method for quickly detecting red blood cells with mutant forms of the PIG-A gene in 100-microliter blood samples. Mutations in the PIG-A gene are an *in vivo* indicator of mutation and can be simply and rapidly quantified using flow cytometry. The new assay should prove useful for DNA damage research, including studies of environmental factors that modify normal rates of mutation.

The researchers extended an approach they previously developed in rodent models to analyze reticulocytes and erythrocytes in human blood. To test the approach, they processed and analyzed three independent blood samples from 52 healthy, nonsmoking adults. They found that the frequency of PIG-A mutant reticulocytes and erythrocytes increased with donor age. Replicate samples showed little variability in the average PIG-A

mutant frequency — about 10 percent for reticulocytes and 2 percent for erythrocytes. However, the researchers observed a thirtyfold range in reticulocyte PIG-A mutation frequency between different donors. They also found that people generally had higher frequencies of PIG-A mutant blood cells than rodents.

The researchers say that this new technique should prove valuable for various biomonitoring applications, including the study of accidental chemical or radiation exposures, occupational exposures, drugs undergoing clinical trials, cancer therapy treatments, and population-based epidemiology studies of environmental exposures.

Citation: [Dertinger SD](#), [Avlasevich SL](#), [Bemis JC](#), [Chen Y](#), [MacGregor JT](#). 2015. Human erythrocyte PIG-A assay: an easily monitored index of gene mutation requiring low volume blood samples. *Environ Mol Mutagen* 56(4):366-377.

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3-D cell culture provides model to study toxicant effects on endocervix

An NIEHS grantee and colleagues are pioneering a method for growing endocervical tissue on scaffolds, creating a 3-D tissue model that can function and interact normally with hormones and other organs. The new model will allow the study of infection and fertility within endocervix tissue in a more physiological way, including how toxicants, drugs, vaccines, and pathogens affect the tissue.

The endocervix tissue lines the cervical canal between the uterus and the vagina, helping to regulate the delicate balance between the tolerance necessary for conception and the protection necessary to keep out pathogens. To create a functional 3-D endocervix tissue culture, the researchers grew human endocervical cells on highly porous polystyrene scaffolds. They used a mixed population of cells that included epithelial and stromal cells.

The researchers assessed how the cultured cells responded to fluctuating levels of the reproductive hormones estradiol and progesterone that mimicked a 28-day menstrual cycle. The cells appeared to function similarly to normal female reproductive organs in that they expressed estrogen and progesterone receptors, proliferated, responded to hormones, produced mucus, and secreted cytokines and growth factors.

Citation: [Arslan SY](#), [Yu Y](#), [Burdette JE](#), [Pavone ME](#), [Hope TJ](#), [Woodruff TK](#), [Kim JJ](#). 2015. Novel three dimensional human endocervix cultures respond to 28-day hormone treatment. *Endocrinology* 156(4):1602-1609.

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Faster assessment of carcinogenic potential for PAH mixtures

An NIEHS grantee and colleagues have developed a faster, more accurate method to assess cancer risk from exposure to polycyclic aromatic hydrocarbons (PAHs). People are primarily exposed to PAHs in the form of mixtures, and this proof-of-concept study demonstrates a first step towards moving away from risk assessments based on individual components of PAH mixtures, to using methods that examine the whole mixture.

To determine the carcinogenic risk of PAH mixtures, the researchers measured the chemical bioactivity profile in skin cells of mice just after short-term PAH exposure. The bioactivity profile, which provides a unique fingerprint of genes and pathways activated by chemicals after exposure, can be used for predicting long-term consequences such as cancer. They tested PAH mixtures found in coal tar, diesel exhaust, and cigarette smoke. After only 12 hours, the researchers could predict the ability of certain PAH mixtures to cause cancer. Other methods take months for tumors to develop.

Although the method needs further testing, the findings demonstrate that long-term cancer outcome for PAH mixtures can be predicted by evaluating bioactivity after short-term exposure. Since the bioactivity profile provides gene signatures that are tied to chemical mechanisms of action, this information could also provide insight into alternate mechanisms of PAH carcinogenesis and related mechanisms for complex mixtures.

Citation: [Tilton SC](#), [Siddens LK](#), [Krueger SK](#), [Larkin AJ](#), [Lohr CV](#), [Williams DE](#), [Baird WM](#), [Waters KM](#). 2015. Mechanism-based classification of PAH mixtures to predict carcinogenic potential. *Toxicol Sci* 146(1):135-145.

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Th17 cells convert into regulatory T cells during immune response

New research, funded in part by NIEHS, shows that the Th17 lineage of T helper cells, which can cause severe human inflammatory diseases, can also differentiate into regulatory T cells to help resolve inflammation. The instability and plasticity of Th17 might offer a new therapeutic target for inflammatory diseases.

The body's inflammatory response to infection is beneficial, but unregulated inflammation can contribute to inflammatory diseases such as rheumatoid arthritis, psoriasis, and multiple sclerosis. Studies have found that Th17 cells show instability, as they can stop expressing their signature inflammatory cytokine IL-17A. They also show plasticity by expressing cytokines typical of other T-cells. To find out if TH17 cells are merely changing expression of a few cytokines or physiologically undergoing a global genetic reprogramming, the researchers developed new fate-mapping mouse models to track Th17 cells during immune responses.

They found that CD4+ T cells that formerly expressed IL-17A go on to acquire an anti-inflammatory phenotype. During an immune response, the TH17 cells showed a change in their signature transcriptional profile and acquired a strong regulatory capacity. The transcriptional profiles of Th17 cells, before and after conversion into regulatory T cells, also revealed a role for transforming growth factor-beta signaling and the aryl hydrocarbon receptor in the conversion process.

The researchers say that the TH17 cell plasticity might be used to develop new and more effective therapies that restore immune tolerance in chronic inflammatory or autoimmune diseases, without the negative side-effects of some systemic immunosuppressive therapies.

Citation: [Gagliani N](#), [Vesely MC](#), [Iseppon A](#), [Brockmann L](#), [Xu H](#), [Palm NW](#), [de Zoete MR](#), [Licona-Limon P](#), [Paiva RS](#), [Ching T](#), [Weaver C](#), [Zi X](#), [Pan X](#), [Fan R](#), [Garmire LX](#), [Cotton MJ](#), [Drier Y](#), [Bernstein B](#), [Geginat J](#), [Stockinger B](#), [Esplugues E](#), [Huber S](#), [Flavell RA](#). 2015. Th17 cells transdifferentiate into regulatory T cells during resolution of inflammation. *Nature*; doi:10.1038/nature14452 [Online 29 April 2015].

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

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Intramural papers of the month

By Tara Ann Cartwright, Monica Frazier, Gabriel Knudsen, Simone Otto, and Qing Xu

- [NTP develops tool to analyze and characterize Tox21 data](#)
- [What's luck got to do with cancer?](#)
- [Calcium sensor protein necessary for the development of psoriasis](#)
- [Heart rate variability in relation to Parkinson disease risk](#)
- [Lack of cross-reactivity between GST allergens could lead to new diagnostic tools](#)

NTP develops tool to analyze and characterize Tox21 data

Researchers at the National Toxicology Program (NTP) recently described a new data analysis pipeline protocol to better characterize high throughput screening data generated in the Tox21 initiative. Tox21 is a collaboration between NIEHS/NTP, the U.S. Environmental Protection Agency National Center for Computational Toxicology, the U.S. Food and Drug Administration, and the National Center for Advancing Translational Sciences. Tox21 seeks to derive a quantitative response for 10,000 pharmaceutical and environmental chemicals for a panel of stress- and nuclear receptor signaling pathway assays using a quantitative high throughput screening approach.

Ideally, active chemicals are both reproducible across experimental runs and relevant to the pathway of interest. However, several challenges to data interpretation exist, from assay artifacts, such as non-reproducible signals, to interfering signals, like autofluorescence. To clarify the signals, a series of noise filtering and data curation protocols were developed in conjunction with a system to identify and flag assay interference. Concentration data were quantified using a weighted area under the curve, resulting in a highly reproducible signal profile, although cytotoxicity was a common confounding factor. In addition, a graphical user interface was introduced that allowed quick evaluation of the Tox21 screenings. **(GK)**

Citation: [Hsieh JH, Sedykh A, Huang R, Xia M, Tice RR](#). 2015. A data analysis pipeline accounting for artifacts in Tox21 quantitative high-throughput screening assays. *J Biomol Screen*; doi:10.1177/1087057115581317 [Online 22 April 2015].

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What's luck got to do with cancer?

Two scientists from the NIEHS Biostatistics and Computational Biology Branch, Clarice Weinberg, Ph.D., and Dmitri Zaykin, Ph.D., wrote a commentary that discussed three inferential pitfalls in a recent article published in the journal *Science*. Their critique considered an analysis by Christian Tomasetti, Ph.D., and Bert Vogelstein, M.D., which documented that on a logarithmic scale, the lifetime risk of cancer in a particular tissue type strongly correlates with the estimated lifetime number of stem cell divisions. These results were widely interpreted as suggesting that most cancers unpreventably occur as a result of bad luck, or errors in DNA replication, with each stem cell division bringing another roll of the dice.

Weinberg and Zaykin illustrated their points using the example of traffic fatalities. They showed how drawing conclusions from correlations based on aggregates of data can lead scientists astray, and offered a compelling argument that the correlation Tomasetti and Vogelstein found did not have implications for the role of genetic or preventable environmental factors. One cannot assign percentages to causative factors, in part because multiple factors often work together. Just as there is much more to traffic safety than the number of miles driven, such as drunk driving or vehicle safety, much of cancer may turn out to be preventable, despite the undeniable role of bad luck. (MF)

Citation: [Weinberg CR, Zaykin D](#). 2015. Is bad luck the main cause of cancer? *J Natl Cancer Inst* 107(7):djv125. (Story)

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Calcium sensor protein necessary for the development of psoriasis

NIEHS researchers have revealed that the calcium sensor protein, stromal interaction molecule 1 (STIM1), plays an important role in the development of psoriasis, a chronic inflammatory skin disorder characterized by plaque-like lesions on the skin. The condition occurs because a large influx of neutrophils enters the epidermis. Mice that lack STIM1 fail to elicit this response, and have less neutrophil infiltration than controls. The study opens a new avenue to treat psoriasis and other immune diseases.

As one of the body's first responders, neutrophils travel toward chemoattractants induced by inflamed skin, using a process known as chemotaxis. In psoriasis, STIM1 facilitates store-operated calcium entry (SOCE) into the cells.

The researchers found that silencing STIM1 in a human neutrophil-like cell line, and removing STIM1 in mouse neutrophils, inhibited chemotaxis, while overexpression of STIM1 enhanced calcium and chemotaxis response to chemoattractants. They also used imiquimod, a topical immune activator, to induce psoriasis-like damage in a mouse model. Compared to control mice, STIM1 knockout mice not only had reduced neutrophil infiltration in the skin, but also had hastened recovery from psoriasis plaques. These results suggest that STIM1 and other SOCE proteins may be potential therapeutic targets for neutrophil-involved disorders. (QX)

Citation: [Steinckwich N, Myers P, Janardhan KS, Flagler ND, King D, Petranka JG, Putney JW](#). 2015. Role of the store-operated calcium entry protein, STIM1, in neutrophil chemotaxis and infiltration into a murine model of psoriasis-inflamed skin. *FASEB J*; doi:10.1096/fj.14-265215 [Online 2 April 2015].

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Heart rate variability in relation to Parkinson disease risk

NIEHS scientists have determined that decreased heart rate variability (HRV) is associated with an increased risk of neurodegeneration in Parkinson's disease (PD), years prior to the manifestation of detectable motor symptoms. In addition to cardinal motor dysfunctions, such as tremor, patients often suffer from a range of nonmotor symptoms. These symptoms may include sleep disturbances, smell and taste dysfunction, constipation, and changes in HRV.

Using data from the 20-year Atherosclerosis Risk in Communities (ARIC) study, the researchers provided the first epidemiological evidence that decreased HRV, a marker of alterations in the cardiac autonomic system, predicts future risk of PD as predicted by the Braak hypothesis. This hypothesis indicates that the Lewy pathology, one of the pathological hallmarks of PD, may start in the olfactory bulb and lower brain stem, and even in periphery nerves, such as the enteric nerve in the gut and cardiac sympathetic or parasympathetic innervations. Research on this pathology and other nonmotor symptoms in the prodromal stage of PD may lead to methods for identifying individuals with higher risk of PD and to a better understanding of disease etiology. (TAC)

Citation: [Alonso A, Huang X, Mosley TH, Heiss G, Chen H](#). 2015. Heart rate variability and the risk of Parkinson disease: The Atherosclerosis Risk in Communities study. *Ann Neurol* 77(5):877-883.

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Lack of cross-reactivity between GST allergens could lead to new diagnostic tools

NIEHS scientists and their collaborators determined that glutathione S-transferase (GST) allergens from cockroach, roundworm, and 2 dust mite species did not contain cross-reactive sites. The discovery was the result of IgE reactivity assays and crystal structure data of allergen GSTs generated by the NIEHS members of the team. The finding is novel because it demonstrates that the allergic response to GST allergens is species-specific, contradicting previous studies that suggested these GST allergens were cross-reactive. Allergists can use the information to offer a more accurate diagnosis of the sensitizing organism and suggest the appropriate treatment.

The research team investigated the IgE reactivity of U.S. patients allergic to cockroach and mite GSTs from 4 species, by comparing the common solvent-accessible areas in the crystal structures that could be responsible for cross-reactivity. The scientists also tested the IgE antibodies from U.S. patients, who are normally exposed to the cockroach and mite allergens, but not the roundworm allergen or the tropical species of mite. These patients allowed the researchers to differentiate the response. IgE antibodies from North American patients were also tested, and they contained antibodies to all 4 GSTs. The scientists concluded the South American patients were cosensitized to all 4 species in their environment, and that specific antibodies to these GST allergens can be used to diagnose the source of an allergy. (SO)

Citation: [Mueller GA, Pedersen LC, Glesner J, Edwards LL, Zakzuk J, London RE, Arruda LK, Chapman MD, Caraballo L, Pomes A](#). 2015. Analysis of glutathione S-transferase allergen cross-reactivity in a North American population: Relevance for molecular diagnosis. *J Allergy Clin Immunol*; doi:10.1016/j.jaci.2015.03.015 [Online 27 April 2015].

(Tara Ann Cartwright, Ph.D., is a former postdoctoral fellow in the NIEHS Intracellular Regulation Group. Monica Frazier, Ph.D., is a former Intramural Research Training Award [IRTA] fellow in the NIEHS Mechanisms of Mutation Group. Gabriel Knudsen, Ph.D., is a research fellow in the National Cancer Institute, Center for Cancer Research, Laboratory of Toxicology and Toxicokinetics. Simone Otto, Ph.D., is an IRTA fellow in the NIEHS Ion Channel Physiology Group. Qing Xu is a biologist in the NIEHS Metabolism, Genes, and Environment Group.)

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Inside the Institute

Preparing for the unthinkable

By John Yewell

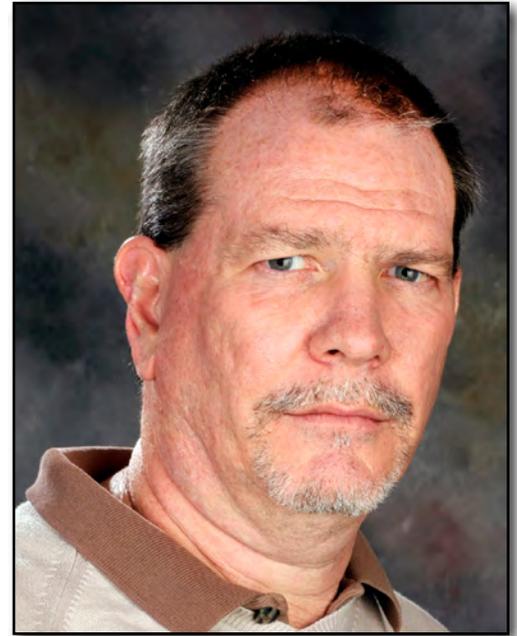
Two people lay wounded as a man with a gun went on a rampage throughout NIEHS June 17 — each person playing a role in an important emergency drill.

Operation Sleipnir attempted to simulate and evaluate the security response to an active shooter scenario. In Norse mythology, Sleipnir is the eight-legged horse belonging to the god Odin. “Like the horse,” explained Mitch Williams, head of the NIEHS Operations and Security Branch, “security is a multi-faceted animal requiring a great deal of coordination for forward progress.”

The NIEHS Operations and Security Branch and the U.S. Environmental Protection Agency (EPA) Facilities Support Branch put four months of planning into the exercise. NIEHS and EPA staff worked alongside Durham County, North Carolina, sheriff and police personnel. Local 911 centers were advised of the exercise in advance.

Morning briefing emphasizes authenticity

Operation Sleipnir kicked off with a morning briefing for the 127 participants. “I’ve heard a little bit of anxiety from some — you’re in good company if you feel this way,” Williams said to the group. “The whole intent here is to learn.”



“The results seem to show that active shooter incidents are on the minds of staff at both campuses, and that continued education of staff on how to react during these types of events will be beneficial,” Williams said afterwards. (Photo courtesy of Steve McCaw)



Security personnel and other participants exchanged notes before the exercise began. “Local law enforcement was involved throughout the planning process to ensure adequate safety protocols and procedures were in place,” Williams said. (Photo courtesy of Robin Macker)

“There will be confusion,” added William Malone, director of global risk services with McManis and Monsalve Associates, with whom NIEHS and the EPA partnered to develop and oversee the exercise. “The goal is to make it as plausible and real as possible.”

The drill was planned to test emergency communications; rehearse coordination among campus guard forces, local police, emergency responders, and NIEHS off-site locations; and practice first aid response. “It’s a learning, no-fault environment,” said Williams during the briefing. “I can’t emphasize that enough.”

Tracking an active shooter

The exercise began shortly after 9:20 a.m., when intercom announcements alerted NIEHS employees to the shooter and instructed them to shelter in place. According to Williams, the scenario involved a hypothetical domestic dispute.

First responders tracked the suspect, played by a Durham police officer, as he headed from one end of the NIEHS main building to the other, then towards the EPA campus. Emergency medical technicians moved in to attend to the simulated victims.

The exercise took twice as long as expected due to the highly complex scenario. “It was stretched to provide ample time for campus security and law enforcement to practice integration and coordination,” Williams said.

Recovery and debriefing key to learning process

The drill concluded with a recovery exercise and debriefing, known as a hotwash, which included all participants involved in the operation. “There was great feedback from NIEHS personnel,” said Darryl Lawton, Malone’s colleague at McManis and Monsalve.

The prediction of confusion was well-founded. Problems with the PA system led to uncertainty about the progress of the exercise, and workers in the offsite Keystone building received no announcements at all.

Despite these glitches, Linda Birnbaum, Ph.D., director of NIEHS and the National Toxicology Program, stressed the value of the exercise. “Overall, I think we evaluated the situation and we learned from it,” Birnbaum said. “We know that the greatest risk in the workplace is an active shooter. And it’s really important that we all know what to do to keep ourselves and our fellows safe in that emergency.”

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



Security closed in on the perpetrator. (Photo courtesy of Steve McCaw)



The orange guns wielded by NIEHS security personnel and other responders helped reinforce the action was a drill. (Photo courtesy of Steve McCaw)



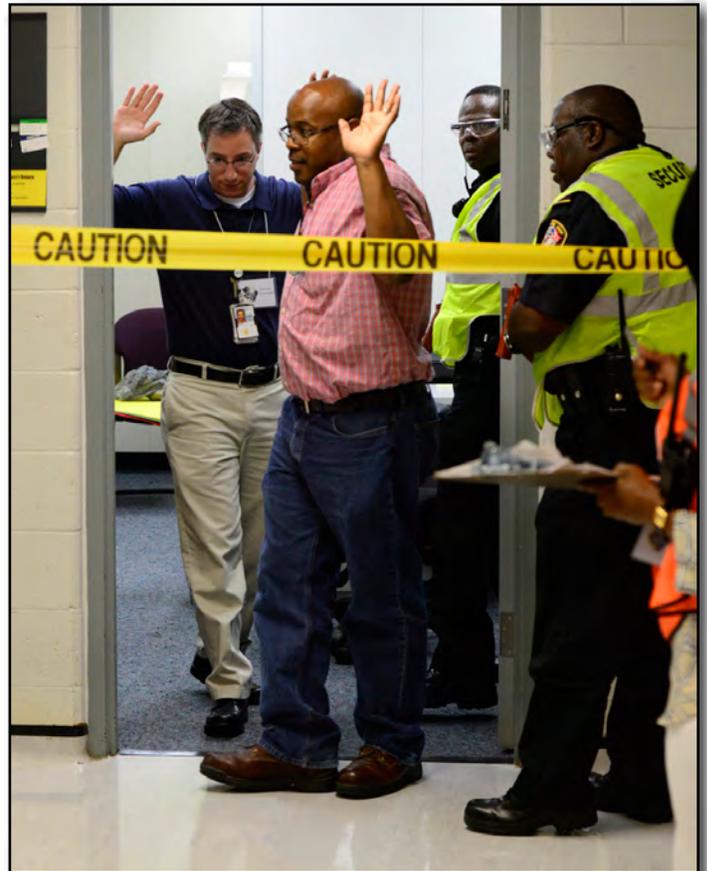
Once the area was confirmed safe, medics were able to attend to a male mock victim. (Photo courtesy of Steve McCaw)



NIEHS personnel attended to a female mock victim. (Photo courtesy of Steve McCaw)



The exercise simulated other hazards associated with a facility attack, such as chemical spills. (Photo courtesy of Steve McCaw)



“The exercise also provided a method for personnel on campuses to practice and discuss safety actions that they may need to take during an active shooter scenario,” Williams said afterward. (Photo courtesy of Steve McCaw)

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