National Institute of Environmental Health Sciences

Environmental Factor

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July 2013

NIEHS Spotlight

Birnbaum headlines Detroit Community Forum Video

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Leaders address Association of Public Health Laboratories Video

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NIEHS spurs investigation into the health effects of e-waste recycling Video

To address the issue on a global level, WHO convened a Working Meeting on E-Waste and Child Health June 11-12 in Geneva.

Scholars Connect program welcomes class of 2013-2014

With its latest group of Scholars Connect student interns, NIEHS tried something a little different — a hands-on laboratory basics boot camp June 3-5.

Agencies award $100,000 to winner of health and technology challenge Video

The winning technology for the My Air, My Health Challenge was announced June 4 at the Health Datapalooza in Washington, D.C.

Science Notebook

Partners launch DREAM Toxicogenetics Challenge

An innovative crowdsourced computational challenge sponsored by NIEHS and partners launched June 11 with an announcement by Sage Bionetworks.

GEMS series highlights mechanisms in the prevention and cure of cancer

The Genetics and Environmental Mutagenesis Society is marking its 31st anniversary in 2013, with an integrated pair of workshops on cancer.

Board advises NTP on critical issues

NTP received both praise and input about how to move forward on several important topics June 25 at its Board of Scientific Counselors meeting.

Early-life traffic-related air pollution exposure linked to hyperactivity

New NIEHS-funded research from the University of Cincinnati finds higher hyperactivity scores at age 7 among children exposed in infancy.

Study links mitochondrial variation with air pollution exposure response

In what the authors believe is the first epidemiological evidence of its kind, a new NIEHS-funded study links mitochondrial DNA with susceptibility to air pollution.

NIEHS Spotlight

Office of Scientific Information Management takes shape Video

NIEHS/NTP Director Linda Birnbaum, Ph.D., addressed a crosscutting theme of the strategic plan with creation of the Office of Scientific Information Management.

NIEHS launches website redesigned for mobile devices

Mobile industry estimates suggest that in the not too distant future nearly everyone in the world will communicate through mobile devices.

WETP workshop identifies strategies to promote effective safety cultures

The NIEHS Worker Education Training Program held a workshop June 11-12 in Washington, D.C., to improve and expand the concept of safety culture.

Former postdoc named chief research officer for NIH research partner

This spring, Rosemarie Ramos, Ph.D., landed a position that combines her research interests in epidemiology with her passion for addressing health disparities.

NIEHS brings public health perspective to climate change policy forum Video

Participating on the prestigious Politics of Climate Change Forum co-sponsored by The New Republic magazine June 19 was NIEHS senior advisor John Balbus, M.D.

Science Notebook

Researchers solve questions about phenobarbital action in the liver

A new study led by Masahiko Negishi, Ph.D., head of the NIEHS Pharmacogenetics Group, was recognized by the Faculty of 1000.

New approach creates red blood cells, platelets *in vitro*

An unlimited number of red blood cells and platelets can be generated from induced pluripotent stem cells *in vitro*, according to a recent study funded in part by NIEHS.

Industry scientist discusses statistical approach to safety testing Video

Joanna Jaworska, Ph.D., a principal scientist with Procter and Gamble in Belgium, visited NIEHS May 20–21, hosted by the NTP alternative methods center.

Synergistic gene-environment interactions increase schizophrenia risk

Using a novel genetically engineered mouse model, NIEHS-funded researchers investigated gene-environment interactions possibly related to mental illness.

Suffering from skin allergies? TRPA1 may be the key to skin relief

Sven-Eric Jordt, Ph.D., has come a long way in studying how certain airborne pollutants interact with sensory nerve cells to cause eye, nose, and throat irritation.

NIEHS Spotlight

Keynote address urges Green Champion winners to raise awareness

John Balbus, M.D., highlighted the important role of NIH and NIEHS in meeting the climate change challenge in a keynote speech at the awards ceremony June 20.

NIH event highlights adverse health effects of bullying Video

NIH observed Lesbian, Gay, Bisexual, Transgender, and Intersex Pride Month June 13 with a panel discussion on bullying across the lifespan.

Inside the Institute

Zeldin urges proactive learning among 2013 summer interns

NIEHS Scientific Director Daryl Zeldin, M.D., urged participants of the 2013 Summer Internship Program to take charge of their educational experience at NIEHS.

Records set on family day at NIEHS

More than 100 youngsters, ranging from toddlers to teens, enjoyed fun, exercise, and creative learning June 20 at NIEHS Bring Your Family to Work Day.

Science Notebook

Crystallography meeting showcases advances in biomedical research

Structural biologists from NIEHS were on hand for the annual Mid-Atlantic Macromolecular Crystallography meeting May 30-June 1 at Duke University.

Risk assessment workshop features cutting-edge toxicogenomic research

Scientists and regulators from around the world met to review progress in safety evaluation strategies and cancer risk assessment May 16-17 in Paris.

This month in EHP

This month, Environmental Health Perspectives celebrates growth in its impact factor and highlights feature stories on sustainable farming and the risks and rewards of nanosilver.

NICEATM/EPA workshop on evaluating cardiovascular safety

The workshop, titled “Translational Alternative Models and Biomarkers Predictive of Drug or Chemical Cardiovascular Risk,” will be held Oct. 10–11 at NIEHS.

Calendar of Upcoming Events

- **July 2,** in the Executive Conference Room, 12:00-1:00 p.m. — Receptor Mechanisms Discussion Group presentation on "Molecular Mechanisms of Steroid Hormone Resistance as Revealed by the Glucocorticoid Receptor," by Priya Ramamoorthy, Ph.D.
- **July 10,** webinar — Partnerships for Environmental Public Health: Oceans and Human Health, register at http://bit.ly/PEPH_Oceans
- **July 15,** iin Rall F193, 11:00 a.m.-12:00 p.m. — Office of Scientific Director seminar by Victoria Seewaldt, M.D., topic TBA
- **July 19,** in Rodbell Auditorium, 10:00-11:00 a.m. — Office of Director seminar on "Carbon Nanotubes Verses Asbestos: Toxicity Concerns," by Qamar Rahman, Ph.D.
- **July 25,** in Rodbell Auditorium, 9:00 a.m.-12:00 p.m. — Summer Internship Program Poster Session
- **July 29-31,** in Rodbell Auditorium — Environmental Health Disparities and Environmental Justice Meeting, contact whitney.freberg@nih.gov to get on waiting list
- View More Events: NIEHS Public Calendar

Extramural Research

Extramural papers of the month

- Teeth analysis reveals early-life dietary transitions
- Nano GO Consortium studies health effects of nanoparticles
- Prenatal BPA exposure alters brain function and behavior in mice
- Dietary nicotine associated with lower Parkinson's disease risk

Intramural Research

Intramural papers of the month

- Ribonucleotides direct the mismatch repair machinery to DNA sequence errors
- Beta-arrestin-2 is major player in development of abdominal aortic aneurysm
- The role of p53 during bacterial pneumonia
- Phenobarbital directly binds to EGFR to activate CAR in the liver

NIEHS Spotlight

Birnbaum headlines Detroit Community Forum

By Eddy Ball

In addition to shrinking population, square miles of dilapidated housing, high unemployment, and a poverty rate of 40 percent, Detroit and southeast Michigan have a large number of major air pollution sources. That made the once proud Motor City a perfect venue for the latest community health forum June 18 featuring NIEHS and NTP Director Linda Birnbaum, Ph.D.

The event was co-sponsored by NIEHS and a University of Michigan (UM) team led by Environmental Health Science Core Center Director Rita Loch-Caruso, Ph.D., Community Outreach and Education Core (COEC) Leader Amy Schultz, Ph.D., and COEC Coordinator Myra Tetteh.

Linked video:

Watch an UM educational video on oxidative stress (05:38)

(Launches in new window)

Download Media Player: Flash

Organizers of the Detroit community forum publicized the event widely in advance, and made exceptional efforts to engage the people of the city's neighborhoods most affected by the adverse health effects of environmental exposures. UM provided transportation from several Detroit locations to the First Congregational Church, where Birnbaum talked with residents. Organizers also provided Spanish, Arabic, and American Sign Language translation, as well as activities for children.

The turnout was impressive, and attendees appreciated the opportunity to learn, and to air their concerns about their health and environment. As one local activist said, "It's good to see scientists, regulators, state officials, activists, and the community together at this forum."

The facility above processes petroleum coke on the Detroit River, depositing piles of waste on the riverbanks. Some of it enters the water as runoff and some is distributed by wind to nearby communities. (Photo courtesy of John Schelp)

The tour stopped at the CHASS Center where Birnbaum, second from left, community leaders, and representatives of nonprofit organizations heard from CHASS Chief Executive Officer Ricardo Guzman, left. (Photo courtesy of John Schelp)

Seeing and listening — the good, the bad, and the ugly

As a prelude to the evening forum, Birnbaum and community leaders took a two-hour tour of the city and its waterfront, to see some of the city's ugly environmental problems, and some of its solutions, firsthand (see slideshow).

Problems included contaminated sites of former tire plants along the waterfront; the high-volume Ambassador Bridge, which carries more than 7,000 trucks daily between the U.S. and Canada; Zug Island, a significant source of industrial pollution along the river; and a 250-acre oil refinery in southwest Detroit.

On a more positive note, people on the tour bus also had the opportunity to see the city's pride and spirit at work at the 982-acre Belle Isle Park; the Earthworks Community Garden, which promotes sustainability and food security for Detroiters; the vibrant Eastern Market; and the federally qualified Community Health and Social Services (CHASS) Center.

Pollution from industrial sites, such as this one near Zug Island, is a source of health and environmental justice concern for nearby residents. (Photo courtesy of John Schelp)

NIEHS investment in Detroit and the state of Michigan

That evening, after thanking the organizing team and the people who turned out to be a part of the community forum, Birnbaum told the audience just how much support NIEHS provides. "Last year, NIEHS funded $2.5 million of research here in Detroit — and more than $18 million across Michigan."

Those millions support a range of research on environmentally related diseases, from infertility, Parkinson's, and autism, to birth defects and a number of cancers. But Birnbaum's remarks soon turned to a persistent concern in the community — respiratory diseases triggered by environmental exposures to industrial chemicals, inhaled fibers and particles, and combustion-related air pollution.

Representatives of city government and the offices of U.S. Congressmen John Conyers Jr. and John Dingell took advantage of an opportunity to talk with Birnbaum, right. (Photo courtesy of John Schelp)

"Take asthma," she told the audience. "It's a complex environmental disease that affects millions of people here and in other states. We fund many studies on asthma and even more on the health effects of air pollution."

She also touched on one of the central themes of the NIEHS strategic plan. "As I see it, environmental health research is the key to preventing disease," she said, " because you can't change your genes, but you can change your environment."

Toward the conclusion of the meeting, one of the community leaders at the forum expressed the sentiment of many attendees. “We need these studies,” he said. “Once we get your research results, we are legit. When I hear that 17 people in one block have cancer, we know there’s a problem.”

The panel included representatives from Michigan state government, community groups, UM, the Sierra Club, and the National Association for the Advancement of Colored People. (Photo courtesy of John Schelp)

Michelle Martinez, of the Consortium of Hispanic Agencies, expressed her group’s reservations about Detroit’s environmental quality. (Photo courtesy of John Schelp)

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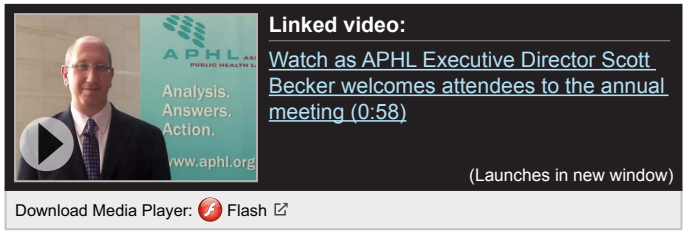
Leaders address Association of Public Health Laboratories

By Michael Heintz

NIEHS and NTP Director Linda Birnbaum, Ph.D., and Director of Extramural Research and Training Gwen Collman, Ph.D., were featured guests at a gathering of environmental health laboratory professionals from the Association of Public Health Laboratories (APHL) on June 4 in Raleigh, N.C. (see text box).

APHL ASSOCIATION OF PUBLIC HEALTH LABORATORIES
www.APHL.org



As part of the APHL Annual Meeting and 7th Government Environmental Laboratory Conference, members of the Environmental Health and Environmental Laboratory Sciences Committees were pleased to host NIEHS leadership for an evening of introductions and discussion. Birnbaum and Collman took the opportunity to familiarize APHL members with the work of NIEHS and NTP. Attendees engaged in a lively discussion following Birnbaum’s review of the newly released NIEHS strategic plan and Collman’s overview of the Institute’s work on exposure science.

As APHL Executive Director Scott Becker said in his introduction, "NIEHS is most certainly a public health agency and one we believe has significant opportunities for future collaboration with environmental health laboratories." Jyl Madlem, laboratory program advisor at the Indiana State Department of Health put it more directly, wondering aloud, "Where has [NIEHS] been all of our lives?"

Birnbaum felt right at home at the APHL meeting, where primary prevention was an overarching theme. (Photo courtesy of Steve McCaw)

Providing the scientific backbone for environmental public health

To answer that question, Birnbaum opened her talk with a discussion of the six themes, 11 goals, and two crosscutting themes of the NIEHS strategic plan. "This is a blueprint for the entire environmental health science community for advancing the basic, clinical, and translational scientific research that can guide the application of public health prevention measures at the grassroots level worldwide," she told the audience, emphasizing the need for scientific excellence to underpin preventive action.

Birnbaum pointed to eight cross-Institute science focus areas where NIEHS-funded research can help inform public health work in the community — epigenetics, inflammation, stem cells, exposome, predictive toxicology, scientific data and knowledge management, website and social media, and global environmental health. According to her, better understanding in each of these areas can translate to practical applications in the field.

Collman's response to the need for APHL to know about NIEHS opened with a discussion of diseases across the lifespan resulting from developmental exposures that can trigger gene mutations and epigenetic modifications. Her discussion of the hidden links of early exposure to conditions that may manifest decades later, in middle or late age, moved into advances in understanding the subtle interactions of genes and environmental exposures in making some individuals more susceptible than others.

NIEHS and APHL — a natural partnership

As a professional association with more than 800 members representing state and local government laboratories, APHL strives for a healthier world through quality laboratory practice. The APHL mission is to promote the role of public health laboratories in shaping national and global health objectives, and to promote policies, programs, and technologies that assure continuous improvement in the quality of laboratory practice and health outcomes. Consisting of government laboratories from across the country, APHL represents the interests of its members through advocacy, policy development, training, networking, and career building.

APHL consists of a number of different scientific programs and committees representing all facets of public health laboratory work. However, the intimate gathering of 25, who heard presentations from Birnbaum and Collman, represented the environmental health program and the two standing committees focusing on testing for chemicals in people and in environmental samples testing efforts. In addition to addressing areas including biomonitoring and responding to chemical threats, these laboratories also test air, soil, and water samples for harmful contaminants.

Collman provided a host of examples of personal sensor developments that are helping establish connections between a specific exposure, such as tobacco smoke, and effects on gene expression profiles, metabolites, protein adducts, DNA adducts and DNA damage, and other health-related outcomes. She pointed to continuing challenges for exposure biology, such as the lack of comprehensive methods to quantify real time and past exposures, and the potentially synergistic effects of mixtures and multiple exposures. "These are fundamental questions to answer as part of the foundation for developing effective public health prevention measures," she said.

Collman discussed NIEHS priorities with APHL environmental committees at their annual meeting. (Photo courtesy of Steve McCaw)

Looking toward future collaboration

The post-presentation discussion covered a wide range of topics, including NIEHS work with genomics, exposure assessments, research centers, community engagement, and opportunities for collaboration in all of these areas with environmental health laboratories. Remarks by Pamela Higgins, Ph.D., special assistant for laboratory operations at the Pennsylvania Department of Environmental Protection, provided information on her laboratory's work connected to hydraulic fracturing in the state. Several other audience members addressed the potential environmental health effects associated with nanomaterials.

By the end of the evening, everyone came away with a sense that environmental laboratories can do more to support the work of NIEHS, including the regional research centers. Sanwat Chaudhuri, Ph.D., bureau director of Chemical and Environmental Services at the Utah Unified State Laboratories, said, "I see that we have many common interests, such as in biomonitoring. This looks like a very promising opportunity to collaborate."

(Michael Heintz, J.D., is a senior specialist with the APHL Environmental Laboratories Program.)

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NIEHS spurs investigation into the health effects of e-waste recycling

By Paula Whitacre

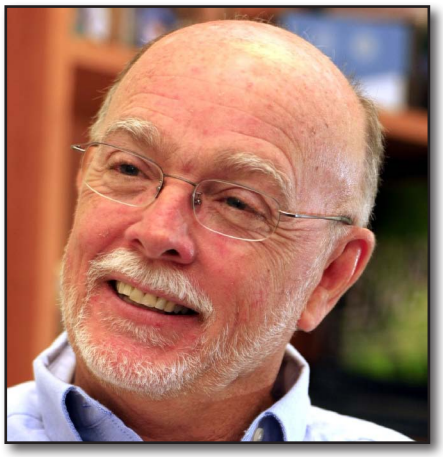
Each new computer innovation or cell-phone upgrade brings progress, but also a problem — a discarded item that becomes part of an exponentially growing electronic waste (e-waste) stream bound for informal, unregulated recycling facilities throughout the world.

To address the issue on a global level, the World Health Organization (WHO) convened a working meeting on e-Waste and child health June 11-12 in Geneva, sponsored by NIEHS and the German Federal Ministry for the Environment, Nature Conservation, and Nuclear Safety. Attendees included experts and other key stakeholders at WHO collaborating centers, other United Nations organizations, and research institutions.

"This work group is so important," said NIEHS and NTP Director Linda Birnbaum, Ph.D., in opening remarks to the participants via a prerecorded video. "It brings visibility to a tremendous worldwide problem. Having this group review the current situation of e-waste exposure in child health, identify research gaps and successful interventions and strategies will determine our next steps."

Birnbaum cited new restrictions on travel by federal employees when she limited the size of the NIEHS delegation. (Photo courtesy of Steve McCaw)

William Suk, Ph.D., director of the NIEHS Center for Risk and Integrated Sciences (CRIS), and staff, as well as NIEHS-supported researchers, were deeply involved in planning and participating in the sessions. In addition, NIEHS provided funds, so researchers from countries where unregulated e-waste recycling is most prevalent — including China, India, Vietnam, and countries in West Africa — could attend.



Suk also directs the NIEHS Superfund Research Program, which has a long history of global health collaboration. (Photo courtesy of Steve McCaw)

Mining e-waste for valuable metals

E-waste is recycled in order to extract gold, copper, platinum, and other commercially attractive materials. While on one level, e-waste recycling sounds commendable economically and environmentally, small-scale sites often engage in hazardous burning, acid baths, and other processes to extract the materials of interest, dumping the rest as waste. Adults and children work and often live amidst the recycling facilities, in direct and indirect contact with a mix of chemicals, including lead and other metals, polybrominated diphenyl ethers (PBDEs), and polychlorinated biphenyls (PCBs).

According to a 2011 Environmental Health Perspectives article (see text box) co-authored by NIEHS grantees Aimin Chen, M.D., Ph.D., and Shuk-mei Ho, Ph.D., pregnant women and children in these communities are at risk of possible changes in fetal and child neurodevelopment. Other health issues, including respiratory irritation and skin burning, have also been observed, leading WHO to develop an initiative on e-waste and children's health.

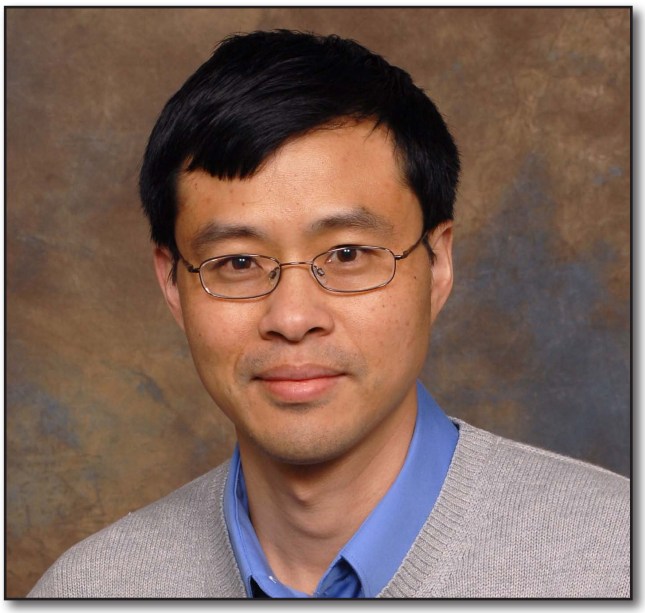
"Children, from newborns through adolescents, represent 26 percent of the world's population, and their potential exposure from what comprises e-waste is a significant health and disease problem as children, and as adults," observed Suk, who served as co-chair of the first day's session with Maria Neira, M.D., director of the Department of Public Health and Environment at WHO. "This meeting was very important for bringing scientists from diverse disciplines."

Moving the conversation forward

To review current knowledge and consider next steps, the approximately 30 participants divided into three groups to discuss exposures, health effects, and interventions. Later, the groups rejoined in a plenary, to recommend areas for research and consider future policies and interventions. According to NIEHS Health Specialist Michelle Heacock, Ph.D., of CRIS, the group agreed that more research is needed to better understand the impact of multiple exposures in an individual.

Next steps include creation of a network of researchers willing to share data and disseminate findings, dedicated sessions on children and e-waste at two major upcoming WHO meetings, and development of a training module for health care practitioners. Publications coming out of the workshop will include a comprehensive review of e-waste and child health, a collaborative paper by the entire workgroup, and an NIEHS-authored white paper describing the discussions and recommendations as they relate to the mission of the Institute.

Heacock said she was moved by the individual narratives of people who lived and worked in the developing countries where e-waste is an increasing problem. (Photo courtesy of Steve McCaw)



The Environmental Factor featured Chen's e-waste research in a January 2011 story. (Photo courtesy of UC)

Research on e-waste and vulnerable populations

An informal survey, conducted in preparation for the WHO working meeting on e-waste and child health, showed that research on the health effects of e-waste recycling is scant.

NIH is currently supporting two studies that focus on children and women.

NIEHS and NTP Director Linda Birnbaum, Ph.D., is part of a team conducting an exposure assessment of home-based, female recycling workers in rural Vietnam, funded by the National Cancer Institute. In 2012, using a control group of women not involved in recycling for comparison, they measured PBDE congeners, other persistent organic pollutants, metals, and other chemicals. Initial biological screening shows dioxins, some PBDEs, and certain metals may be elevated in the recycling workers, with additional analyses under way.

Aimin Chen, M.D., Ph.D., of the University of Cincinnati College of Medicine, is focusing on pregnant women and their infants in Guiyu, China, an area with a large, concentrated amount of e-waste recycling being conducted in thousands of small family-run workshops. Working with Xia Huo, M.D., Ph.D., of Shantuo University Medical College in China, he is looking at exposure levels in the women and in a control group, their fetuses, and infants.

The next NIEHS Global Environmental Health (GEH) newsletter will focus on Chen's research in Guiyu. For more information on the newsletter and other global environmental health activities supported by NIEHS, visit the GEH website.

Piles of e-waste await processing by employees in a small workshop in Guiyu, China. (Photo courtesy of Xia Huo)

Participants at the WHO working meeting on e-waste and child health identified research gaps and called for greater awareness of the health impacts of e-waste recycling. (Photo courtesy of Xia Huo)

Citation: Chen A, Dietrich KN, Huo X, Ho SM. 2011. Developmental neurotoxicants in e-waste: an emerging health concern. Environ Health Perspect 119(4):431-438.

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

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Scholars Connect program welcomes class of 2013-2014

By Eddy Ball

With its latest group of Scholars Connect student interns, NIEHS tried something a little different this year — a hands-on laboratory basics boot camp June 3-5, to give participants momentum as they begin their year of training and mentorship in Institute labs.

Unlike a military boot camp, the NIEHS Scholars Connect Program (NSCP) Science Training Workshop relied on positive reinforcement and personalized instruction. The workshop featured a two-hour small group review of the principles of molecular biology and one-hour review of scientific methods and units, followed by two full days of one-on-one instruction on laboratory applications of scientific method, with the very tools and procedures bench scientists use every day in their experiments.

The workshop was developed by Huei-Chen Lao, a biologist on detail as science education and outreach coordinator in the NIEHS Office of Science Education and Diversity (OSED), and conducted by eight volunteers. NIEHS staff scientist Elena Braithwaite, Ph.D., of the Comparative Genomics Group, and seven postdoctoral fellows, made up the instructional team.

Representing a range of research interests, the fellows included Aleksandra Adomas, Ph.D., of the Eukaryotic Transcriptional Regulation Group; Miranda Bernhardt, Ph.D., of the Reproductive Medicine Group; Qing Cheng, Ph.D., of the Ion Channel Physiology Group; Jackson Hoffman, Ph.D., of the Chromatin and Gene Expression Group; Sabrina Robertson, Ph.D., of the Developmental Neurobiology Group; Misty Thomas, Ph.D., of the Macromolecular Structure Group; and Wipawee (Joy) Winuthayanon, Ph.D., of the Receptor Biology Group.

As Lao explained, "The lab component of the workshop covered reagent preparation, constructing a standard curve, and using the standard curve to determine the protein concentration of the unknown samples; restriction enzyme digestion of DNA; and gel electrophoresis to separate DNA and protein molecules." Lao said, she hopes the training gave the six undergraduates, participating this year from universities in the Raleigh/Durham, N.C., area, a head start when they entered their labs.

Oyelowo practiced careful release of liquid in her pipette. "Draw the liquid in very slowly," instructor Winuthayanon told the interns, "so you don't contaminate the pipette." (Photo courtesy of Steve McCaw)

Instructor Adomas reviewed the basics of the metric system, with special emphasis on the measurements most frequently used in laboratory experiments. "This is something that will become second nature for you," she said. (Photo courtesy of Steve McCaw)

With a student-teacher ratio of almost one to one, the scholars received as much personal attention as they needed. Cheng, left, helped Dunigan as she worked with the conversion-volume formula. (Photo courtesy of Steve McCaw)

Part of the NIEHS mission — to increase diversity in the biomedical workforce

Now in its second year, NSCP is aimed at increasing diversity in the environmental health sciences. According to OSED Director Ericka Reid, Ph.D., the program is designed to enhance scientific training for highly motivated science, technology, engineering, and math (STEM) undergraduate students from surrounding Historically Black Colleges and Universities, and other nearby academic institutions with underrepresented minority student populations.

Intern Cathy Jamison is assisting with NSCP and will work closely with the scholars, who will train in NIEHS research groups full time this summer and part time during the fall and spring semesters. Participants, this year, are rising juniors and seniors in STEM programs at Saint Augustine's University (SAU), North Carolina Central University (NCCU), North Carolina State University (NCSU), and the University of North Carolina (UNC) at Chapel Hill (see text box).

Participants will devote 40 hours per week to training this summer, and may participate in NIH Summer Internship Program activities, including a poster presentation at the end of the summer program. During the 2013-2014 academic year, the scholars will spend up to 20 hours on research-related activities, each week, as paid interns, while they continue their academic programs at their home institutions. Research-related activities include laboratory work mentored by lead researchers, scientists, and postdoctoral fellows, along with literature reviews, participation in lab meetings, and attendance at research workshops and seminars.

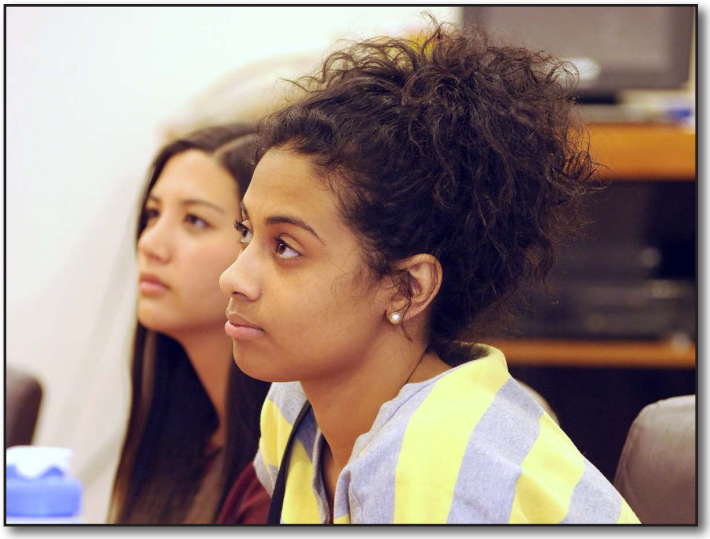
The program requires interns to participate in weekly NSCP professional development seminars, where they engage in dynamic dialogues with NIEHS scientists on environmental health research topics. The seminars also aim to further the scholars' scientific development, through research-relevant software training, in preparation for presenting findings from their own scientific research at the NSCP spring symposium The symposium represents the culmination of three semesters, or connections, of defining a research project, constructing an appropriate hypothesis, and conducting experiments to test that hypothesis.

The 2013-2014 scholars

- **Kate Blatchford**, who studies nutrition science at NCSU, is a part of the NTP Molecular Pathogenesis Group headed by Darlene Dixon, D.V.M., Ph.D.
- **Mia Burks**, who is a public health major at SAU with a minor in biology, is working with Clarice Weinberg, Ph.D., chief of the Biostatistics Branch.
- **Brittany Dunigan**, who studies biology at SAU, is the newest member of the DNA Repair and Nucleic Acid Enzymology Group headed by Samuel Wilson, M.D.
- **Ashley Kang**, who studies polymer and color chemistry and medical sciences at NCSU, works with Xiaoling Li, Ph.D., head of the Metabolism, Genes, and Environment Group.
- **Melissa Kerr**, a chemistry student at NCCU, is part of the Matrix Biology Group, headed by Stavros Garantziotis, M.D.
- **Toyosi Oyelowo**, who studies environmental health science at UNC, works with the NTP Neurotoxicology Group led by Jean Harry, Ph.D.

On their final day of training, the scholars completed a post-workshop assessment and enjoyed a visit from NIEHS and NTP Director Linda Birnbaum, Ph.D., standing left, and Reid. (Photo courtesy of Steve McCaw)

Lao, left, wrapped up the training with a group discussion of the connections between best laboratory practices and the scientific method. (Photo courtesy of Steve McCaw)



Kang, left, and Burks listened, as fellow students responded to Lao's questions. (Photo courtesy of Steve McCaw)

NSCP participants, shown in lab coats, joined their instructors during a break in the lab training. Seated on the first row are Blatchford, Burks, and Oyelowo. Standing, left to right, are Winuthayanon, Adomas, Robertson, Hoffman, Kerr, Dunigan, Cheng, and Lao. Not shown: Braithwaite, Bernhardt, Kang, and Thomas. (Photo courtesy of Steve McCaw)

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Agencies award $100,000 to winner of health and technology challenge

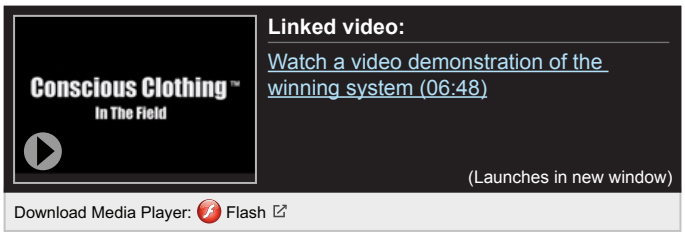
By Christine Flowers

New technology that creates a personal, portable, and wearable air pollution sensor, developed under the My Air, My Health Challenge, was announced June 4 at the Health Datapalooza in Washington, D.C. The grand prize of $100,000 was awarded to Conscious Clothing.

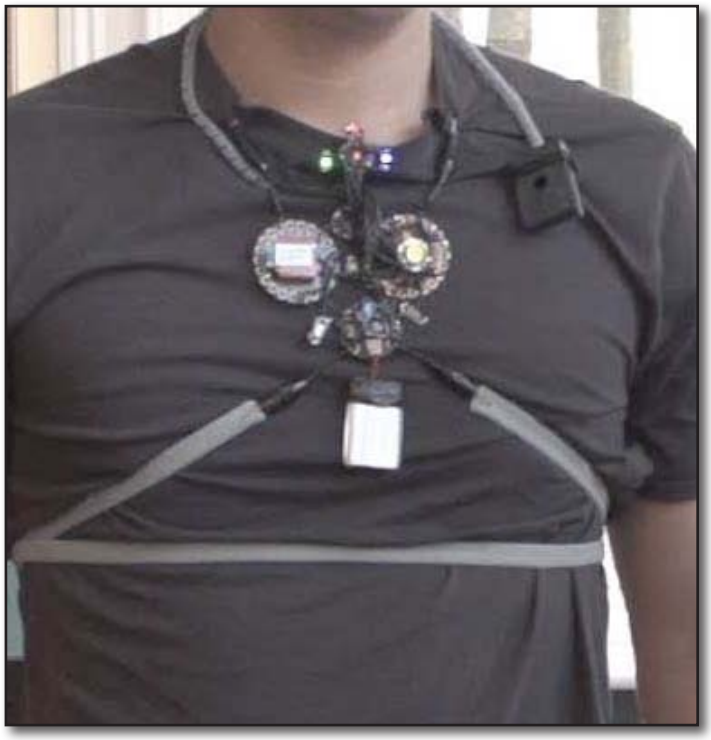
The challenge was held by the National Institutes of Health, the Office of the National Coordinator for Health Information Technology of the U.S. Department of Health and Human Services, and the U.S. Environmental Protection Agency (EPA).

Health Datapalooza is intended to encourage innovation and partnerships between technology specialists and health professionals, to further biomedical research and solve health problems. Conscious Clothing's design was chosen from four finalists.

The winning team of three New England-educated scientists created the Conscious Clothing system, a wearable breathing analysis tool that calculates the amount of particulate matter that is inhaled. The system uses groove strips, stretchy, conductive strips of knitted silver material wrapped around the ribcage, to measure breath volume, and collects and transmits data in real time, via Bluetooth, to any Bluetooth-capable device.



The competition kicked of June 6, 2012, with announcements by Birnbaum and Paulson (see story) at the Health Data Initiative Forum in Washington, D.C.



According to the developers, the Conscious Clothing system is lightweight, flexible, and comfortable. Users require no additional training in order to fit the apparatus themselves. (Photo courtesy of Conscious Clothing)

Tapping the potential of personal sensors

"With people wearing these new data-collecting devices, researchers will be able to see and understand the relationships between varying levels of air pollutants and individual health responses in real time. This is a big step toward treating and, more importantly, preventing disease and illness," said NIEHS and NTP Director Linda Birnbaum, Ph.D. "This is an exciting time in research."

"This integration of technologies represents a growing area of interest for environmental and health scientists," said Glenn Paulson, Ph.D., EPA science advisor. "We're at the edge of a technology wave where anyone can use these sensors. The potential impact on personalized health and local environmental quality is tremendous."

"The finalists for this challenge demonstrate that health information technology can range from personal, wearable sensors to integrated hospital electronic health record systems," said National Coordinator for Health Information Technology (IT) Farzad Mostashari, M.D. "The benefits of health IT, whether being worn by a single person or managed throughout a large hospital, will have similar results in helping keep people healthy."

NIEHS program administrator David Balshaw, Ph.D., who oversees exposure biology grants, emphasized that the winning technology is a first prototype. "As the Conscious Clothing team refines the design and capabilities of the system, it will become far less obtrusive," he said. "The essential components are very low burden and can be integrated directly into, for instance, exercise clothing with essentially no impact."

David Kuller of AUX, Gabrielle Savage Dockterman of Angel Devil Productions, and Dot Kelly of Shearwater Design, developed the Conscious Clothing system. Kuller, the lead inventor, is a 1982 graduate of the Massachusetts Institute of Technology, where he worked in the institute's media lab in its earliest days. Dockterman is a 1983 graduate of Harvard University, and Kelly, the team chemist, earned her bachelor's degree from Yale in 1980.

In a scene from the Conscious Clothing video, inventor David Kuller wears the technology. The only part of the system visible to an observer is the matchbook-sized air sensor above the collar. (Photo courtesy of Conscious Clothing)

For more information about the winning design, visit the My Air, My Health Challenge Web page.

(Christine Flowers is the director of the NIEHS Office of Communications and Public Liaison.)

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Office of Scientific Information Management takes shape

By Eddy Ball

Knowledge management is a crosscutting theme of the 2012-2017 NIEHS strategic plan. With approval in June from NIH, NIEHS and NTP Director Linda Birnbaum, Ph.D., is proceeding with implementation of the Institute's Office of Scientific Information Management (OSIM). Director Linda Birnbaum, Ph.D., announced creation of the NIEHS Office of Scientific Information Management (OSIM). She charged the new office with facilitating a more collaborative approach to science through data sharing and identifying the technology infrastructure required to enhance data analysis and discovery.

Birnbaum named NIEHS senior advisor Allen Dearry, Ph.D., as OSIM director. Dearry will coordinate efforts of three staff — Data Scientist Rebecca Boyles, Informationist Stephanie Holmgren, and Library Manager Erin Knight.

As Dearry explained, "Changes in technologies and methods have shifted the bottleneck in scientific productivity from data production to data management, communication, and interpretation."

"All of us, no matter what field of biomedical research we are in, are inundated with data," Dearry explained. "This situation presents the intramural and extramural communities with challenges in terms of collecting, storing, managing, and disseminating data effectively."

By creating this new office, NIEHS is establishing itself alongside other NIH and federal information science activities. OSIM staff members, along with others across the Institute, are representing NIEHS on workgroups to develop new trans-NIH data science policies and initiatives. Dearry serves on the NIH Big Data to Knowledge executive committee and is co-chairing the interagency Networking and Information Technology Research and Development Program's Big Data Senior Steering Group.

Dearry, who has served as acting associate director of NTP and led several research translation initiatives, said he looks forward to leading the OSIM initiative. (Photo courtesy of Steve McCaw)

Data coordination

The ultimate goal of data coordination and sharing is to maximize NIEHS and NTP research investments, greatly increasing discovery of how the environment influences human health and disease. As data scientist, Boyles will begin by helping to establish a trans-NIEHS scientific data council. She will also assess the scope of NIEHS data sets, tools, and management practices.

"Environmental sciences data encompasses a very broad range of data types from biological and genetic data, to environmental and population information," Boyles said. "This presents a special challenge for determining collection protocol, tagging or identifying data, and making data accessible to the scientific community."

As scientists engage in research using massive quantities of data, better tools for data curation and analysis will make it easier for them to see patterns that emerge from their data, and then to make quality judgments about what those patterns mean.

Boyles joined NIEHS this year, specifically to head the OSIM data coordination effort. "Data coordination is really a new activity, and it will be a major focus within OSIM as a whole," Dearry said. (Photo courtesy of Steve McCaw)

Embedded informationists

An informationist is someone who has a combined knowledge of library science and biomedical subject matter, and is embedded in a group to provide information services tailored to meet that group's specific research needs. Holmgren, who served as acting director of the NIEHS Library for two years, started as an informationist in 2006. In her new role with OSIM, she will provide comprehensive literature searches, identification and evaluation of new databases and research tools, and assistance with content management. Holmgren will also develop a program to train research, policy, and program staff interested in becoming informationists within their groups.

Library Services

As a foundational element of OSIM, Knight and her staff are at the forefront of providing modern-day library services to the Institute's scientists, and can help researchers navigate the vast amount of information available to them.

The NIEHS Library continues to evolve from its traditional print model to a more online presence, offering NIEHS staff access to electronic resources, including more than 6,000 e-journals and 1,500 e-books, as well as many scientific databases. Professional librarians continue to provide reference and document delivery assistance, literature searches, and instruction on e-resources that will help researchers save time and money. The library professionals are also available for help with special projects and one-on-one consultations.

Like other activities of OSIM, the NIEHS library will increasingly reach out to NIEHS scientists and administrators, in order to ensure the library collection and services continue to evolve and stay relevant for the benefit of the Institute. Library staff will also work closely with, and support, the data science and informationist programs.

"I look forward to the contributions of this new office. It will help us meet the challenges of information science, research collaboration, and data-driven environmental health research," Birnbaum said.

Holmgren has worked as an embedded informationist since 2006 (see story). NIEHS first introduced the concept, which is based on a clinical model, during the tenure of former library Branch Chief Dav Robertson. (Photo courtesy of Steve McCaw)

Knight became manager of the NIEHS library in 2012 (see story) and assembled a staff of two other librarians. (Photo courtesy of Steve McCaw)

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NIEHS launches website redesigned for mobile devices

By Eddy Ball

Like it or not, mobile devices are taking over world communications, and organizations that want to get their messages out are having to adapt. Mobile industry estimates suggest that, in the not too distant future, nearly everyone in the world will communicate through cell phones, tablets, and other mobile devices.

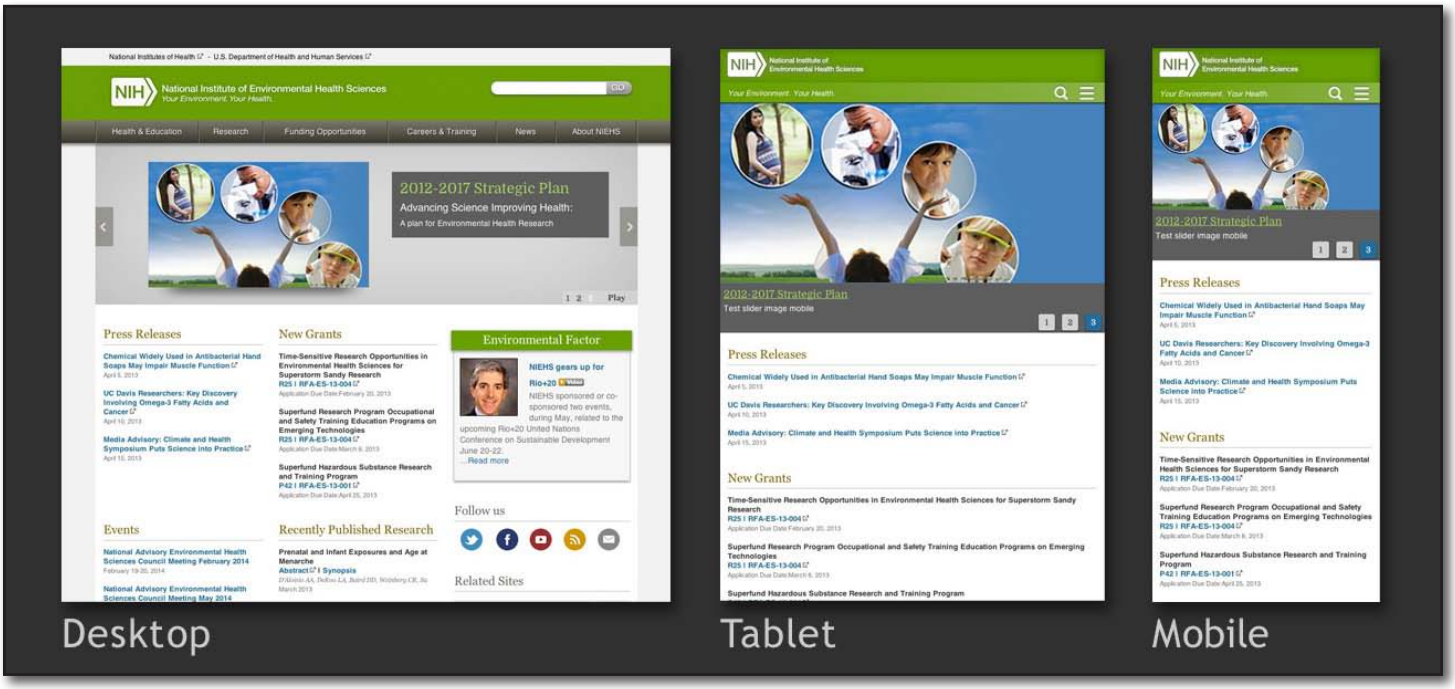
NIEHS took a huge step forward June 28 by launching a redesigned public website that is easily viewed and navigated on a broad variety of mobile devices, such as smart phones and tablets. This new responsive Web design gives the Institute a distinct advantage in its efforts to reach the billions of people worldwide who experience the Web on a small screen — and may not use or even have access to a desktop computer.

"Our responsive website will help us meet the environmental health needs of a changing world," said NIEHS Communications Director Christine Flowers. "We're one of the first organizations of our kind to address this communications challenge." While people everywhere are going mobile, Flowers added, the growth is greatest in the developing countries where NIEHS global environmental health research is especially relevant.

Flowers credits her team, including NIEHS Web manager Cheryl Thompson, digital information specialist Joe Poccia, and information technology specialist Sharon Hite for their leadership and technical expertise in completing the challenging project.

A new look for mobile users

To experience how much a responsive website changes the landscape for visitors to NIEHS public Web pages, it's helpful to see how the pages appear on different devices. While the content remains the same, whether it's accessed on a 27-inch desktop screen or 2.44-inch wide mobile display, the arrangement changes automatically for optimal viewing.



With the NIEHS responsive website capability, the landscape changes, but the message comes across in its entirety. Sizes shown above range from a 1024-pixel wide desktop monitor screen, left, to a 244-pixel wide cell phone display, right. (Graphic courtesy of Joe Poccia)

Instead of simply shrinking a Web page to fit a screen — much the way widescreen films are truncated to fit the standard television screen — the NIEHS responsive website is capable of reformatting the page for mobile devices, to retain virtually all the information seen on a desktop monitor. Buttons are also larger and easier to touch with fingers, and graphics are used judiciously to save mobile users precious bandwidth.

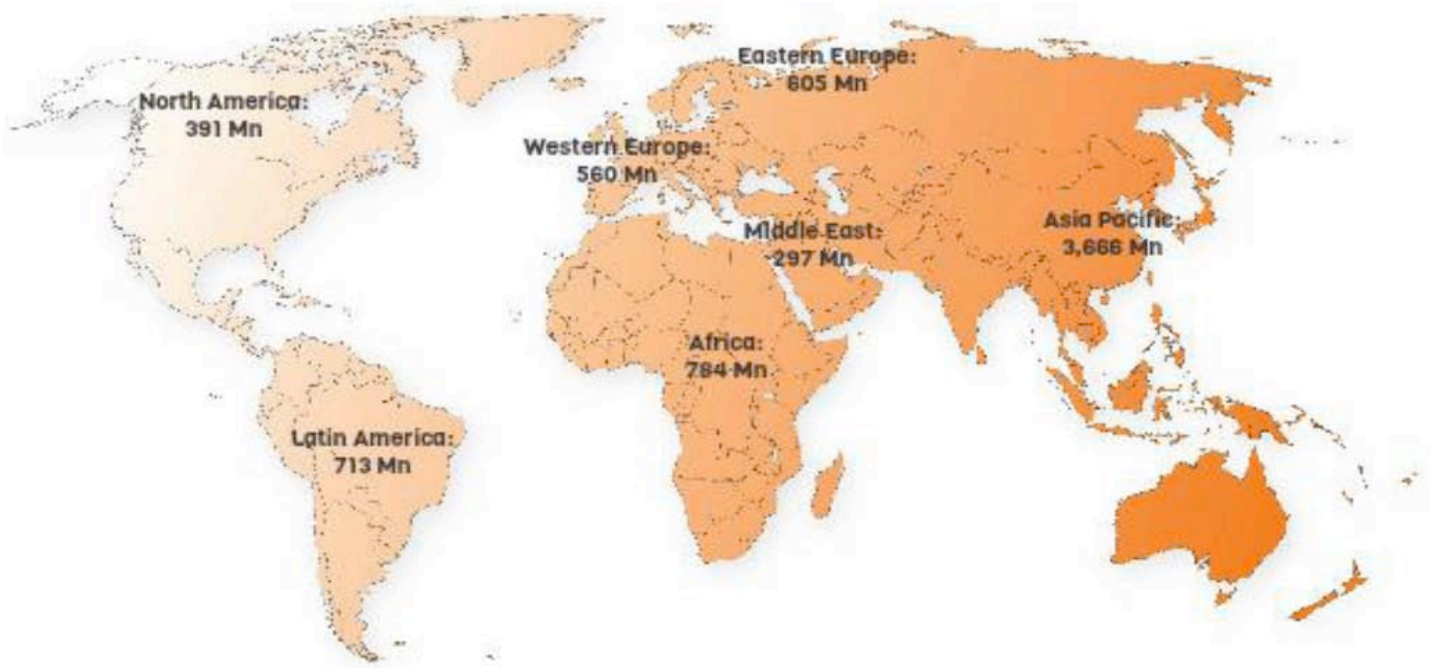
According to Thompson, the majority of the public website is now available in responsive format, and the remaining public pages, such as the Environmental Factor newsletter and Kids' Pages, are in development.

Playing by the numbers

According to industry estimates reported in the Portio Research Mobile Factbook 2013, the worldwide mobile subscriber base was expected to reach 6.5 billion by the end of last year, taking global mobile penetration to approximately 92 percent of the world's population. The subscriber base is forecast to increase at what the industry is calling a compounded annual growth rate (CAGR) of 7.3 percent between 2011 and 2016, to reach nearly 8.5 billion by end of 2016, with growth led by markets in Asia Pacific and Africa.

Although population estimates vary according to the model used (see ScienceDaily story), the number of people on earth could reach as high as 15 billion by mid-century, with the greatest increases in developing countries. If CAGR increases continue as anticipated, even more of the world's people will be getting their information on the small screen, and responsive website capability will become more important than ever as a tool for effective communication.

Figure 3: Mobile Subscriber Base – Regional (In Million, 2013F)



Source: Portio Research Ltd.

F – Forecasted

The growth in use of mobile devices is greatest in the very countries where desktop ownership is likely to be lowest — and the need for reliable information about global health issues the most pressing.

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WETP workshop identifies strategies to promote effective safety cultures

By Ryan Campbell

The NIEHS Worker Education and Training Program (WETP) held a workshop June 11-12 in Washington, D.C., to improve and expand the concept of safety culture, and identify challenges and solutions to ensure worker protection. Approximately 130 grantees, experts, and contractors attended the meeting, a workshop organized and co-sponsored by the National Institute for Occupational Safety and Health (NIOSH) and CPWR – The Center for Construction Research and Training, an NIEHS WETP grantee.

Hecker, at the podium, gave a brief history of safety culture, putting safety culture into perspective with a look at how research findings inform the understanding of safety culture and climate. Stafford, right, gave the welcome remarks June 11 and introduced the shared plenary session speakers. (Photo courtesy of Ted Outwater)

WETP Director Chip Hughes introduced the first guest speaker, Mark Griffon, a member of the U.S. Chemical Safety Board (CSB), as an avid supporter of worker safety and health, including his work with WETP grantees. As Griffon explained, "Safety culture is a term being used too loosely, and it [tends to be used to] blame the worker. Safety culture should look at an organizational structure, and the intended happening versus what happened, and why decisions were made the way they were" (see text box).

Guest speaker Griffon offered insights into how effective an organization's safety culture is, based on findings from CSB investigations. (Photo courtesy of Ted Outwater)

Looking for solutions by identifying the causes of poor safety culture

Griffon highlighted several factors contributing to a poor safety culture, such as a lack of safety management leadership, discouraging injury and illness reporting, infrastructure failures, and the absence of responses to worker feedback, which are factors the CSB has identified in past facility accidents and disasters.

David Michaels, Ph.D., assistant secretary of labor for occupational safety and health at the Occupational Safety and Health Administration, called for action to further support positive safety cultures. "Employers control the workplace, so we must have them on board. We need to push from a compliance culture to a health and safety management culture," he said. Employee injury and illness programs support a robust safety culture and they help save lives, and help companies save money, Michaels continued.

WETP grantee Judith Daltuva, of the University of Michigan (UM) School of Public Health, moderated a panel discussion of a case study on an organization that successfully overcame barriers while building its own safety culture. Representatives from The International Union, United Automobile, Aerospace and Agricultural Implement Workers of America (UAW); UM; and the Ford Motor Company were able to create a confidential system for workers to report safety concerns, as part of an initiative to improve Ford's safety culture, capture worker injuries and concerns, and mitigate potential hazards.

Coordinating different safety cultures

WETP staff members Jim Remington, Ted Outwater, and Sharon Beard led breakout sessions exploring how safety culture operates during disasters at U.S. Department of Energy cleanup sites, and on overcoming barriers to worker involvement. During disasters, difficulty emerges regarding consistent messaging about hazards related to response efforts coordinated by federal, state, and local authorities. The dissemination of consistent health and safety information is complicated by the fact that each federal agency and contractor brings its own safety culture to disaster and cleanup areas. A common theme among the breakout sessions was that workplaces often emphasize metrics and production over safety. Many times, safety is stated as a priority, but, in practice, production rates and time constraints often outweigh concerns about worker safety.

In his remarks concluding the conference, NIOSH Director John Howard, M.D., underscored the important role of research in supporting the themes discussed during the two-day workshop. Howard concluded that blame-free environments must be created and supported, and that when resources are committed, safety cultures can and do succeed. When organizations truly share the core values of a good safety culture, they are more likely to find a consensus when they need to cooperate in an emergency situation.

(Ryan Campbell is on the staff of MDB, a contractor for the WETP and NIEHS Superfund Research Program.)

Toward a definition of safety culture

CPWR Executive Director Pete Stafford introduced the concept of safety culture and said, "In planning this workshop, we realized there are many views of safety culture. There are [also] other industries with a different view and strong beliefs about safety culture."

In the workshop's opening plenary session, University of Oregon Associate Professor Emeritus Steve Hecker explained that the concept of safety culture is often misunderstood, and that it and the concept of safety climate need to be more clearly defined, because the terms are not interchangeable and one concept should not be more highly valued than the other. Hecker stressed, "Safety culture and climate are measurable and can have value as indicators." As indicators, they can measure supervisory safety support, safety competence levels, and work pressure and safety.

Stafford and Hecker agreed that safety culture is a macro-scale term, referring to a subset of an organization's overall culture and reflecting its mindset toward all of its operations. Safety climate, in contrast, more often refers to the transient, situation-specific or team-specific atmosphere that may or may not accurately reflect the organization's overall cultural values. If the organization is committed to safety, the climate of a specific situation can be changed relatively quickly to better conform to an organization's culture. In contrast, changing culture involves a much more difficult and time-consuming effort to fundamentally reshape attitudes from the boardroom to the workroom floor.

During the workshop's closing plenary, CSB Chairman Rafael Moure-Eraso, Ph.D., reiterated the need to properly define safety culture, and emphasized the complex relationship between the organization's culture and its safety performance. "Safety culture is not always a culture of safety," he said. Safety culture is a characteristic of an organization with an overriding commitment to safety.

Don Elisburg, senior advisor for the NIEHS National Clearinghouse, gave the charge to track-session breakout groups, as Michaels, seated, pondered his upcoming presentation on promoting safety culture.
(Photo courtesy of Ted Outwater)

Daltuva is regarded as one of the top safety program evaluators in the U.S. She is research area specialist at UM and a contractor for evaluation of training for UAW.
(Photo courtesy of Ted Outwater)

In their roles as ranking government safety officials, Moure-Eraso, left, and Howard were natural choices for closing presentations to inspire attendees to work toward deeper commitments to quality safety culture in the workplace.
(Photo courtesy of Ted Outwater)

Hughes adjourned the workshop on June 12. He had also moderated the annual WETP Awardee Meeting June 10.
(Photo courtesy of Ted Outwater)

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Former postdoc named chief research officer for NIH research partner

By Eddy Ball

Former NIH health disparities trainee Rosemarie Ramos, Ph.D., has landed a position that combines her research interests in epidemiology with her passion for addressing health disparities. In May, Ramos was selected as the founding chief research officer for CommuniCare — a network of U.S. Department of Health and Human Services-supported community health centers headquartered in San Antonio.

In addition to her full-time duties as the NIEHS health disparities fellow, Ramos was co-chair of the NTA steering committee, served on the Diversity Council's Hispanic Heritage Committee, contributed to the Environmental Factor, and hosted guest lectures on women's health and endocrine disrupting compounds, and healthcare/prevention outreach in Hispanic communities along the U.S.-Mexico border. (Photo courtesy of Steve McCaw)

A key objective for Ramos, in carrying out a collaborative research agenda at CommuniCare, will be utilization of the community engagement infrastructure developed through the NIH Clinical and Translational Science Awards (CTSA) program. Preexisting community engagement infrastructure within CommuniCare includes many providers, patients, and community leaders who are always seeking ways to improve chronic disease diagnosis, treatment, and prevention.

"The organization is among the first community health centers in the nation to invest in a research division," Ramos said, "and I am humbled to have been selected for the position … It's a perfect fit for my personality, research interests, and commitment to public health."

Building partnerships in the community

Ramos has already identified CTSA-affiliated, practice-based research networks that have expressed interest in being partners in CommuniCare's research agenda. These partnerships will also align with the mission of the NIH National Center for Advancing Translational Sciences, to generate innovative methods for enhancing the implementation of diagnostics and therapeutics across a wide range of human health needs, diseases, and conditions.

CommuniCare is a pioneer in this effort, since no other community health center in Texas has attempted to establish a research office. Ramos considers herself to be well suited for leading this pioneering effort, due to her training under NIEHS Director Emeritus Kenneth Olden, Ph.D., a mentor she considers to be a true pioneer in the area of collaborative research to reduce health disparities. Building on her doctorate in epidemiology and her master's in public health from the University of Pittsburgh Graduate School of Public Health, her fellowship training honed her skills for establishing the foundation for fruitful research in a community health setting.

CommuniCare's logo and slogan communicate its dual focus on prevention and treatment for the entire community — "For All. For Life. Para Todos. Por Vida."

Career development at NIEHS and beyond

While at NIEHS, Ramos was active in the NIEHS Trainees Assembly (NTA) and career development programs organized by then Office of Fellows' Career Development (OFCD) Director Diane Klotz, Ph.D., experiences that served her well as she negotiated the winding career path back to her geographical and professional roots (see stories).

According to Ramos, without access to NIEHS-sponsored career development, she would not have pursued the varied post-training career opportunities that enabled her to be competitive for her new position. Although the job market is a tough climate, Ramos explained, it can be successfully navigated by the NIEHS trainee, because of the exceptional training environment at the Institute. She advised current trainees to take full advantage of what's available and "Use it to the max!"

Ramos completed her NIH health disparities fellowship in 2008, following Olden's move to create a new school of public health at the City University of New York (CUNY), and returned to her hometown of San Antonio to work with public health consultant Fernando Guerra, M.D., director of health for the San Antonio Metropolitan Health District (Metro Health) and a colleague of Olden's. In her role as public health project advisor for Metro Health, Ramos supported the pilot phase of the San Antonio A1C diabetes registry. Upon completion of this pilot project, she joined the epidemiology division of the U.S. Air Force School of Aerospace Medicine, which has received NIEHS funding for projects related to Agent Orange exposure.

In 2011, Ramos assumed the role of senior scientist within the U.S. Air Force Medical Service Office of the Chief Scientist. During this time, she supported the residency research program and served as a subject matter expert and co-researcher for several U.S. Department of Defense clinical and injury outcome studies.

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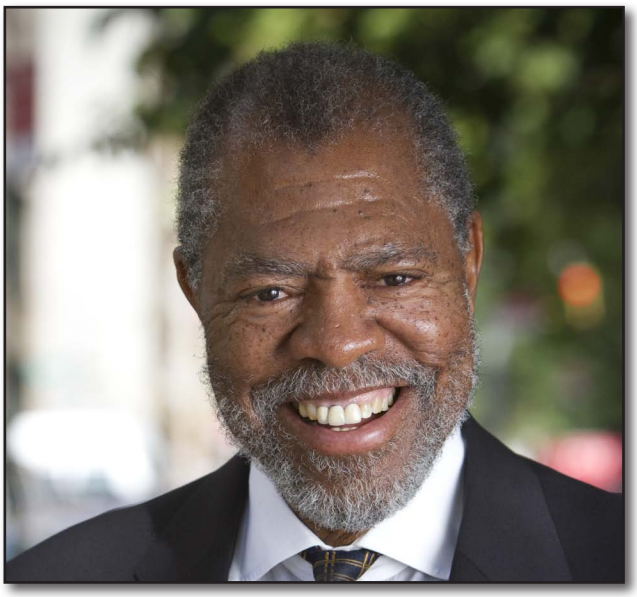


Olden continued to serve as a long-distance mentor, as he worked in New York and later Washington, D.C., where he now heads the U.S. Environmental Protection Agency National Center for Environmental Assessment. (Photo courtesy of CUNY)

A former NIEHS postdoc herself, Klotz was head of OFCD during the final two years of Ramos' training. "She is a great mentor," Ramos said. (Photo courtesy of Steve McCaw)

NIEHS brings public health perspective to climate change policy forum

By Pamela Kidron

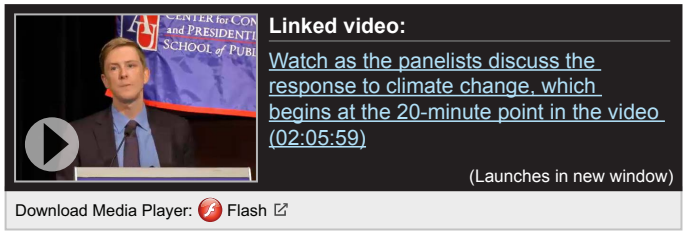
NIEHS Senior Advisor for Public Health John Balbus, M.D., participated in the prestigious Politics of Climate Change Forum June 19 in Washington, D.C., co-sponsored by The New Republic magazine and the American University School of Public Affairs (AUSPA) Center for Congressional and Presidential Studies.

Balbus joined other key experts and observers of the climate change issue, such as Deputy Assistant to the President for Energy and Climate Change Heather Zichal, The New Republic Publisher and Editor-in-Chief Chris Hughes, and AUSPA Dean Barbara Romzek, Ph.D.

Balbus explained the impact of climate change on public health, stressed the importance of better communicating climate change-related health issues to the public, and pressed for more attention to the anticipated long-term health effects of climate change.

How climate change impacts health

In the panel discussion "Rethinking Our Response to Climate Change: Policy Advice from Beyond the Beltway," Balbus explained how changes in temperature can affect pollen numbers, how differences in water temperature and air temperature can affect the transmission of waterborne and fruitborne diseases, and how extreme events can influence mental health. Hurricanes Katrina and Sandy, for example, have been associated with post-traumatic stress disorders. Some effects are not as well-studied as others, he added.



The panel included, from left, moderator Jonathan Cone, senior editor of The New Republic; Dan Lashof, Ph.D., director of the climate and clear air program at the Natural Resources Defense Council; Balbus; and Anne Kelly, director of public policy at Ceres. (Photo courtesy of Christopher Parks)

Balbus said that despite a large body of knowledge firmly establishing that climate change threatens public health, the implications of that threat have yet to be embraced by the public.

"For years, the discourse on climate change has led people to think that climate change is a problem somewhere else, like the arctic, for something else, like a polar bear, or in a country that you will never go to in your life," said Balbus.

Some communication researchers now favor personalizing and localizing the effects of climate change, continued Balbus, by showing, for example, how air pollution may affect the health of children with asthma, or how heat stress induced by elevated temperatures could impact grandparents with heart disease. He also pointed to a body of research that shows threats and negative impacts fail to mobilize people. Recent, preliminary research is looking at positive health messages, including what good can come from actually taking action on climate change.

Balbus pondered his response to Cone's question about public perception of climate change issues. (Photo courtesy of Christopher Parks)

Long-term impacts

Balbus advocated for addressing not only short-term, but also long-term changes. There is much that can be done, such as reducing air pollution in the short-term to protect the public from some of climate change's milder impacts, he said. But addressing the root causes of air pollution is the type of long-term change that can be transformative.

"What gives public health officials pause to think are the possible long-term effects decades from now, such as the inability to feed a population of nine billion or the problem of living in coastal areas where there is massive sea level rising," said Balbus.

The panelists were remarkably poised, especially considering the brilliant stage lighting on the set. (Photo courtesy of Christopher Parks)

Public awareness

Responding to a question about why it is taking so long for the public to widely acknowledge that climate change threatens health, Balbus said the subject has yet to significantly enter such public discourse as media coverage, and it takes a long time from the point when the science on a subject is strong enough, to the point the general public accepts it as established fact and acts on it. "We are just not there yet," he said.

(Pamela Kidron is a contract writer with the NIEHS office in Bethesda, Md.)

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Keynote address urges Green Champion winners to raise awareness

By Pamela Kidron

Calling global climate change one of the greatest challenges of this generation, NIEHS Senior Advisor for Public Health John Balbus, M.D., highlighted the important role of the National Institutes of Health (NIH) and NIEHS in meeting that challenge, during a keynote speech June 20 at the 2013 HHS Green Champion Award ceremony on the NIH campus in Bethesda, Md.

Balbus is an advocate for addressing the public health impact of climate change. (Photo courtesy of Ernie Branson)

The Green Champion Award recognizes U.S. Department of Health and Human Services (HHS) employees for efforts to reduce greenhouse gas emissions, energy and water consumption, and pollution.

"Today our Green Champions are truly champions, because they are helping us take on this great challenge of our lifetime — the related challenges of sustainability and climate change resilience," said Balbus. "Innovations in reducing energy and water consumption, like those we honor today, do not merely produce environmental benefits and lower costs. These sustainability measures are all public health interventions."

Addressing climate change

NIH and NIEHS have had a longstanding leadership role in addressing health implications of climate change, Balbus said. NIEHS scientists, for example, have helped lead efforts to coordinate research on the human health effects of climate change across the US government and internationally. NIEHS currently is heading an NIH pilot grant program on the health implications of climate change, including waterborne diarrheal diseases and heat-related deaths.

Helping the public understand

Balbus concluded by urging the crowd to take on three challenges.

First, was the need to take sustainability and climate resilience to the next level in order to fully meet the challenges that lie ahead. The second was to do so in a way that recognized economic constraints.

"I encourage us all to continue to be creative and look for transformative innovation wherever we can," said Balbus, "but we also need to be creative in figuring out how to make the transformations with minimal costs or cost savings."

Lastly, Balbus said that many still do not understand how climate change is tied to the nation's health. He called on those in the room to help the general public and their own colleagues understand these linkages. In closing, he noted, "we will need many more hands on the oars to fully succeed."

(Pamela Kidron is a contract writer with the NIEHS office in Bethesda, Md.)

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NIH event highlights adverse health effects of bullying

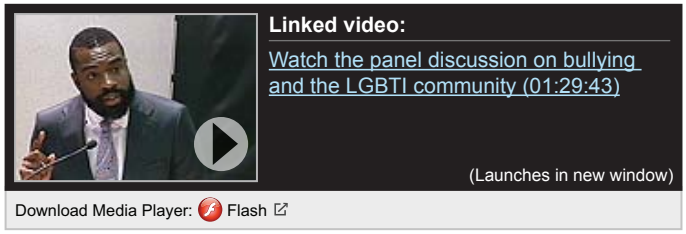
By Eddy Ball

NIH observed Lesbian, Gay, Bisexual, Transgender, and Intersex Pride Month June 13 with a panel discussion on bullying across the lifespan, "Painting Kinder Tomorrows … Today: Eliminating Bullying Through Education, Practice, Research, and Advocacy." The program took place in Natcher Auditorium on the NIH campus in Bethesda, Md., and was webcast for employees at other locations, including NIEHS.

Hosting the event was the NIH Office of Equal Opportunity and Diversity Management (OEODM) Lesbian, Gay, Bisexual, Transgender, and Intersex (LGBTI) Special Emphasis Program (SEP), in collaboration with Salutaris, the NIH LGBT Employees' Forum; and LGBT Fellows and Friends.

The program opened and concluded with remarks by OEODM Director Debra Chew, who introduced NIH Principal Deputy Director Lawrence Tabak, D.D.S., Ph.D. Expressing the NIH leadership's commitment to diversity and LGBTI health research, Tabak reflected on how bullying has evolved in the world of electronic communications.

"Bullying, unfortunately, has [also] changed with the times … We've always had bullies …, but now we've got online bullying, virtual bullying, social media bullying, and messaging bullying," Tabak said. "What does it say about us and the world, if we don't get a handle on this?"



Trying to get a handle on bullying — at school, at work, in the community

Moderator and discussant Darnell Moore, a writer and LGBT social activist living and working in New York, helped to give bullying a personal dimension, by setting the stage for a poetry reading by LGBTI SEP Manager Albert Smith Jr. on how it feels to be a victim. The persona of "Colored Homicidal" by youth slam poet Kai Davis is a young lesbian girl, who is physically abused and humiliated to the point that she is driven to self-loathing and ultimately violence of her own. The poem's theme is simple, but moving and relevant — verbal and physical violence begets pain, and one outlet for pain is to perpetuate a cycle of even more violence and suffering.

"Today we commemorate the men and women around the world who identify themselves as LGBTI," Chew said, as she described what she called the "NIH diversity fabric." She described Tabak as a champion of the LGBTI community and of diversity at NIH. (Photo courtesy of NIH)

In his introduction, Tabak described new developments in addressing LGBTI health concerns, including an updated nondiscriminatory policy that specifically includes LGBTI employees, a trans-NIH committee on LGBTI research, and a series of active listening sessions at NIH beginning June 27. (Photo courtesy of NIH)

The impressive group of panelists included Arnold Grossman, Ph.D., professor of applied psychology at New York University; Mark Hatzenbuehler, Ph.D., professor of sociomedical sciences at Columbia University; Erin Reiney, director of the Bullying Prevention program at the Health Resources and Services Administration; and Jessica Hawkins, a coordinator with NIH CIVIL, a resource that promotes a healthy and safe workplace, and helps prevent workplace violence.

Bullying across the lifespan

Presentations by the panelists ranged from Grossman's studies of elderly gay men, to Hawkins' work to reduce bullying in the workplace by co-workers and supervisors. Most of the presentations, like Hatzenbuehler's studies of the effects of anti-bullying programs in the public schools of Oregon, raised as many questions as answers, pointing to just how much research still needs to be done.

Because the victims, both LGBTI and straight, have until recently been in the closet about the psychological, social, workplace, and health effects of verbal and physical abuse, not even the experts are completely sure of the extent of the human suffering and economic impact involved. In schools, bullying can affect educational outcomes for victims in ways not fully understood, and, as Hawkins explained, no one yet knows how extensively bullying shapes absenteeism and productivity in the workplace.

Reiney had a list of best practices to share with her colleagues and the audience. While her program calls for consistent, long-term interventions, she, like Hawkins, cautioned against zero tolerance policies. As obviously wrong as the abuse perpetrated by bullies is, in a sense, bullies are also victims of the very fear, hatred, and violence they practice. According to Reiney, some might profit from a chance to experience disciplinary consequences that are corrective, as well as punitive, to become part of a solution.

"We are gathered here to discuss the real time effects of bullying," Moore said in his opening remarks. "It is an act that produces a range of affective and psychological effects. It produces shame." (Photo courtesy of NIH)

Smith was obviously moved by the words of the Kai Davis poem describing how tormentors typecast and bullied the persona. "I never asked to be a rainbow. They colored me homicidal." (Photo courtesy of NIH)

Hatzenbuehler thanked NIH for supporting his studies on bullying in Oregon's public schools. (Photo courtesy of NIH)

"This is a long road," Reiney said of her agency's campaign. "Ultimately, it needs to become uncool to bully." (Photo courtesy of NIH)

Seated at the panel, from left, are Grossman, Hatzenbuehler, Hawkins, and Reiney. "Early intervention is key," Hawkins told the audience. "If you see things, speak up." (Photo courtesy of NIH)

Grossman explained that elderly LGBTI people spent decades learning to be as invisible as possible, and their health issues have not been studied extensively. "[But] they do exist, and they do need services," he said. (Photo courtesy of NIH)

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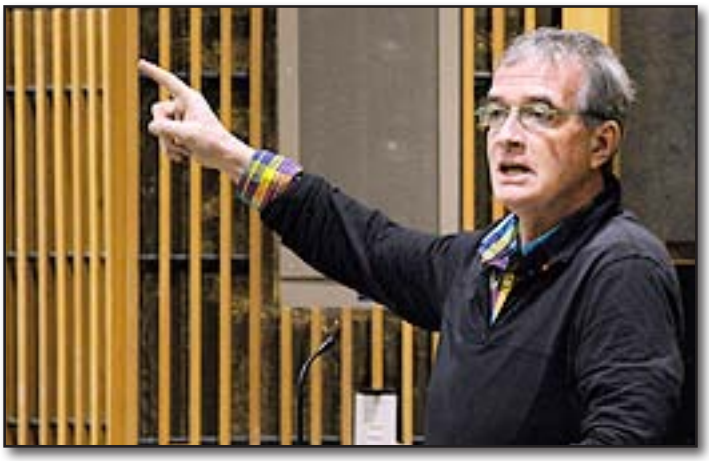
Science Notebook

Partners launch DREAM Toxicogenetics Challenge

An innovative crowdsourced computational challenge, the DREAM Toxicogenetics Challenge, launched June 11 with an announcement by Sage Bionetworks. The goal of the three-month challenge is to find better ways to predict the toxicity of chemicals, to increase understanding of how a person's individual genetics can influence cytotoxic response of exposure to widely used chemicals.

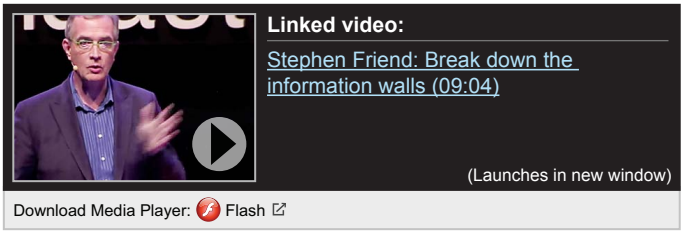


Co-founder, president, and director of Sage Bionetworks Stephen Friend, M.D., Ph.D., explored the challenge concept during a talk at NIEHS (see story) earlier this year. (Photo courtesy of Steve McCaw)

The challenge is being led and organized by scientists from Sage Bionetworks, DREAM (Dialogue for Reverse Engineering Assessments and Methods), the University of North Carolina at Chapel Hill (UNC), NIEHS, and the NIH National Center for Advancing Translational Sciences (NCATS). These groups have generated population-scale toxicity data in a human *in vitro* model system.

The partners utilized human cell lines from the 1000 Genomes Project, which consists of correlated genomic data and cell lines collected from individuals representing nine distinct populations with defined genetic heterogeneity. The NIEHS-NCATS-UNC team has conducted the largest ever population-based *in vitro* cytotoxicity study, by evaluating the extent of cytotoxicity induced by 179 common pharmaceutical or important environmental chemicals in 1086 human lymphoblastoid cell lines. The challenge is asking a wide range of researchers to use the genomic and cytotoxicity data to build models that can predict variation in individual response to a chemical, based on genomic data.

Challenges such as this engage diverse communities of scientists to competitively solve a specific problem in a given time period, by placing scientific data, tools, and the resulting predictive models into an open commons or workspace — in effect, crowdsourcing data analysis.



Those interested in participating in this challenge, and two others, can sign up at a dedicated Web page. The challenge will close on Sept. 15 and the top-scoring team(s) will be announced at the sixth annual RECOMB/ISCB conference on Regulatory and Systems Genomics, with DREAM Challenges, Nov. 8-12 in Toronto.

A big data approach to understanding chemical toxicity

"Predicting how different people or groups of people will respond to certain chemicals is difficult to determine, but important for protecting the public's health," said Raymond Tice, Ph.D., who heads the NTP Biomolecular Screening Branch at NIEHS and is leading an NTP initiative to develop a paradigm of predictive toxicology using high-throughput screening. "This challenge represents a novel partnership and a novel approach to addressing, more effectively and efficiently, big data problems in environmental health science," added Allen Dearry, Ph.D., director of the NIEHS Office of Scientific Information Management, which coordinated interaction with Sage/DREAM.

"We are delighted to partner with Sage/DREAM, to release this unique dataset obtained through a broad partnership with NIEHS and NCATS," said Ivan Rusyn, M.D., Ph.D., professor of environmental sciences and engineering at the UNC Gillings School of Global Public Health. "The collaboration with Sage/DREAM is an important extension of our ongoing partnership with NIEHS and UNC," added Anton Simeonov, Ph.D., NCATS acting scientific director of discovery innovation.

This is the type of challenge that all of the partners are most interested in running — those with the potential to provide powerful scientific insights and meaningful public impact. Toxicity testing that monitors health risks posed to humans through chemical exposure is a crucial component of public health. Yet, for every chemical that has been tested for toxicity, there are thousands that remain untested.

To address this backlog, toxicologists are interested in leveraging the dramatic technological advances in molecular biology and computer science that now make it possible to use high throughput *in vitro* biochemical and cell-based assays with banks of genomic data for toxicological testing. The challenge aims to advance the pace of using and analyzing such complex data, in order to accelerate the generation of useful information for the scientific and public health communities.

Tice is the NTP lead on the Tox21 consortium, a partnership of NIEHS, the U.S. Environmental Protection Agency, U.S. Food and Drug Administration, and NIH Chemical Genomics Center. (Photo courtesy of Steve McCaw)

Dearry provides leadership in the effort to define, plan, and evaluate scientific data and knowledge management approaches in environmental health. (Photo courtesy of Steve McCaw)

Rusyn is a long-term NIEHS grantee and a leader in the field of toxicogenomics. (Photo courtesy of UNC)

Simeonov is a key member of the NCATS team of scientists conducting clinical and translational research to transform laboratory discoveries into new therapies for patients. (Photo courtesy of NIH)

Challenges open June 11 to Sept. 15

The NIEHS-NCATS-UNC DREAM Toxicogenetics Challenge is one of three challenges that Sage Bionetworks and DREAM opened to the public. The two other challenges involve breast cancer networks and whole cell model parameters.

- **The Heritage Provider Network-DREAM Breast Cancer Network Inference Challenge** —Participants in this challenge will be provided with an extensive proteomics time-course dataset on four breast cancer cell lines and tasked with analyzing these data to solve three sub-challenges — building network models that represent the active cell signaling pathways in breast cancer; predicting the dynamic response of various phospho-proteins to drug perturbations; and proposing novel strategies to visualize these high dimensional data.

- **The Whole-Cell Parameter Estimation DREAM Challenge** — Participants will be provided with a whole cell model of the sexually transmitted pathogen *Mycoplasma genitalium* and tasked with estimating the model parameters, from simulated data, for specific biological processes. The simulated data to be provided represents possible measurements in actual experiments, as participants interact with a credit system to purchase this data on demand, with the aim to refine the parameters under estimation.

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GEMS series highlights mechanisms in the prevention and cure of cancer

By Richard Sloane

The Genetics and Environmental Mutagenesis Society (GEMS) is marking its 31st anniversary in 2013, with an integrated pair of workshops on cancer.

GEMS, led this year by President Tom Hughes and President-elect William Kaufmann, Ph.D., held its spring symposium May 21 at the Environmental Protection Agency (EPA) in Research Triangle Park (RTP), with a program of talks on "Mechanisms of Environmental Carcinogenesis." Six scientists from North Carolina's major biomedical research centers explored the latest developments in basic research on ways environmental exposures trigger DNA mutagenesis and damage responses that can cause cancers and promote their spread throughout the body.

The group will take the bold next step with its fall meeting Oct. 23 at the Sheraton Imperial Hotel in RTP. The ambitious program on "Exploiting the DNA Damage Response to Prevent and Cure Cancer" will feature presentations by leaders in the field of cancer prevention and treatment. Speakers scheduled to present include Aziz Sancar, M.D., Ph.D., from the University of North Carolina at Chapel Hill (UNC) School of Medicine; William Gmeiner, Ph.D., of the Wake Forest University (WFU) School of Medicine; and pediatric cancer specialist Michael Kastan, M.D., Ph.D., of the Duke University Cancer Institute.

As it has in past years, the GEMS fall meeting will also highlight talks by enthusiastic students and postdocs, with a travel award to a national meeting for the best talk and a cash award for the best poster presentation.

Looking at mechanisms

"Most of us are concerned about cancer," said Kaufmann, as he opened the spring symposium. "Why are certain agents making us, our children, and our parents sick, and giving us cancer?" Kaufmann said, it is our mission to resolve this question through our research, and we need to accurately translate and apply the latest basic mechanistic research, if we really want to prevent and cure cancer.

NC biomedical researchers and GEMS — marking 31 years together

GEMS is a regionally active group of interested environmental scientists, toxicologists, and geneticists sharing a common interest in the interplay of genetics and the environment.

The group holds two meetings each year, one in the spring and a larger event in the fall that features talks and poster session competitions for students and postdoctoral fellows. The programs usually draw upon the considerable talent from North Carolina's major biomedical research centers, but each year's president-elect, who designs the workshops, may also reach farther from home to schedule leading authorities on specific topics from across the U.S. to participate.

To find out more about upcoming programs sponsored by GEMS, or to join the group, visit the group's Web page. GEMS actively promotes the involvement of students and postdocs, by offering annual memberships for just $15.00. Regular membership costs $25.00, annually, and a lifetime membership is available for just $125.00. GEMS encourages participation by minority groups, women in science, people with disabilities, and other historically underrepresented groups.

As he welcomed attendees to the spring meeting, Hughes thanked GEMS members George Woodall and Carol Schwartz for making it possible to stream the symposium for remote viewing by people at local universities. (Photo courtesy of Steve McCaw)

Possible environmental mutagens abound, from ultraviolet radiation to computer tomography (CT) scan radiation, to arsenic and pesticides, and the symposium's speakers addressed many of them. Robert Smart, Ph.D., of North Carolina State University, stated that nonmelanoma skin cancers occur more frequently in humans than do breast, prostate, lung, and colon cancers combined. The NIEHS grantee explained that UVB exposure adversely affects the S phase of the cell cycle, the point at which genes replicate. A person's genetic makeup and age act as compounding factors.

Arsenic, a well- known toxicant, is now recognized as a mutagen, by its ability to induce chromosome instability during mitosis, explained EPA's Andrew Kligerman, Ph.D., in his exploration of its mode of action. WFU's Mark Miller, Ph.D., threw suspicion on the safety of X-ray computed tomography, or CT scans, which he said may act as a promoter of carcinogenesis, an adverse effect that for some patients may actually outweigh the value of CT scans in early detection.

In Miller's studies, tumor incidence in mice increased after CT exposures comparable to what humans receive. Further study will be needed to determine the specific human risks.

Other speakers included Cyrus Vaziri, Ph.D., of UNC, who presented his recent findings on the integration of translesion synthesis with checkpoint signaling and cell cycle progression, and Michael Goldstein, Ph.D., of Duke, who addressed nucleolin mediation of nucleosome disruption and promotion of DNA double-strand break repair.

In his opening remarks at what was GEMS first entirely free symposium, Kaufmann cautioned the audience that childhood UVB exposure, resulting in sunburn, is a precursor of malignant melanoma. "One of the best things you can do is protect the little ones," he said. (Photo courtesy of Steve McCaw)

A new concept in cancer development — mutational clusters

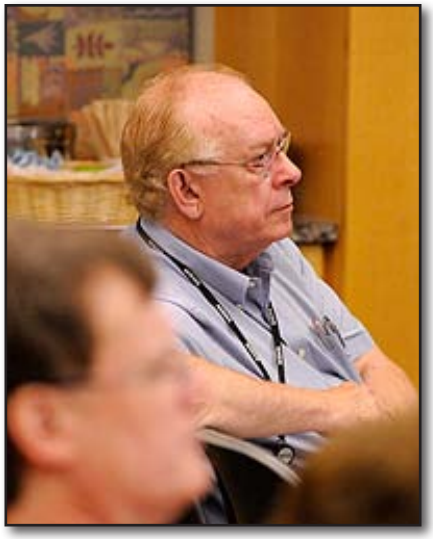
Dmitry Gordenin, Ph.D., a yeast genetics expert in the NIEHS Laboratory of Molecular Genetics, explained that mutations are typically perceived as random, independent events. However, he observed nonrandom clustered mutations, also called mutational showers, made at transient single-strand DNA, near DNA double-strand breaks and at replication forks, in yeast.

According to Gordenin, mutation rate in cluster can exceed the average rate across the genome by a hundred-fold or more, and generate genetic variants at a rapid rate. Importantly, clusters also occur in sequenced human cancers. Gordenin presented analysis indicating that APOBEC cytidine deaminases, enzymes that normally act in anti-viral innate immunity, are a source of mutations in clusters, as well as across cancer genomes. A better understanding of clusters may provide important clues regarding pathways leading to rapid genetic variation and instability, which in turn leads to cancer.

Smart's lab has studied a family of CCAAT/ Enhancer Binding Proteins (C/EBP), which serves as a master regulator of cell cycle exit and terminal differential. He said C/EBP is inactivated in numerous cancers. (Photo courtesy of Steve McCaw)

(Richard Sloane is an employee services specialist with the NIEHS Office of Management.)

Gordenin, who was born in Soviet-era Russia, quipped that DNA mutations leading to cancer are all equal in their ability to lead to cancer, but, as in socialism, some are just more equal than others. (Photo courtesy of Steve McCaw)



Many of the GEMS faithful, including NTP geneticist Jack Bishop, Ph.D., were on hand for the talks. (Photo courtesy of Steve McCaw)

Likewise, NTP biologist and veteran GEMS member Diane Spencer was sure to make this spring's symposium. (Photo courtesy of Steve McCaw)

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Board advises NTP on critical issues

By Robin Mackar

NTP received both praise and input about how to move forward on several important topics, including systematic review, Tox21, and several cancer listings, June 25 at its Board of Scientific Counselors (BSC) meeting.

New BSC Chair Melissa McDiarmid, M.D., from the University of Maryland, started the meeting with a report from NIEHS and NTP Director Linda Birnbaum, Ph.D. Birnbaum updated the board on recent activities, including the NIEHS strategic plan, budget, science findings, and some recently launched big data initiatives, including the NIEHS-NCATS-UNC DREAM Toxicogenetics Challenge that had more than 60 people signed up the first week.

Lunn, who leads the RoC effort, made two presentations to the board — one focused on a new draft concept, and the other on progress of two RoC candidate substances. (Photo courtesy of Steve McCaw)

NTP monograph

Kembra Howdeshell, Ph.D., from the NTP Office of Health Assessment and Translation (OHAT), provided an overview of the NTP Monograph on Developmental Effects and Pregnancy Outcomes Associated with Cancer

Chemotherapy Use During Pregnancy. Howdeshell made her presentation by phone, since she was also presenting the monograph in a symposium on cancer and pregnancy at the Teratology Society annual meeting, co-chaired by Howdeshell and Michael Shelby, Ph.D., also of OHAT.

Howdeshell said that 457 observational studies were included in the evaluation, which was developed to serve as a tool for physicians and patients making clinical decisions about cancer treatment during pregnancy.

McDiarmid, who served as the BSC liaison during the peer review of the monograph in October 2012, told the board that NTP did a good job given the limitations of the data. NTP and the board identified the need for greater participation in registries, and improvements in the quality of reporting in case reports.

Contracts approved

The BSC also unanimously approved two contract concepts — quality assessment support and global pathology support.

Report on Carcinogens

Ruth Lunn, Dr.P.H., director of the Office of the Report on Carcinogens (RoC) shared where NTP was in the development of the next RoC. After presenting a schematic of how the NTP reaches its level of evidence conclusions, she focused on the substances 1-bromopropane and cumene, which were peer reviewed at a public meeting in March 2013. Lunn summarized the comments from the panel and shared NTP's response. The peer review panel concurred with NTP to list both substances as reasonably anticipated human carcinogens.

BSC member Dale Hattis, Ph.D., of Clark University, who served as BSC liaison for the peer review meeting, commented on how thorough he felt the discussions were at the meeting and how receptive NTP was to the comments provided.

Highlights of NTP Roadmap progress

The NTP associate director's report focused on progress made by NTP since it laid out its roadmap in 2004. Bucher framed his talk around three of the main areas addressed in the plan, with a heavy emphasis on Tox21:

- Refine traditional toxicology assays
- Develop rapid mechanism-based predictive screens for environmentally induced diseases
- Improve the overall utility of NTP products for public health decision making

Bucher talked about how, in Phase II of Tox21, a 10,000-compound library had been tested across a set of nuclear receptor and stress response pathway assays, in a small number of assays. He showed data where compounds with similar biological activity patterns, across the different assays, were linked in a connectivity network.

"Using this kind of plot helps us determine if some of the associations we are seeing make sense," Bucher said. "We are just at the beginning stages, but eventually we hope to get to a point where the Tox21 data can be used to better predict the potential for hazard and, thus, protect public health.

A lively discussion followed the presentation, with encouragement from BSC to continue to move forward with testing in human cells. "In every case we can, we're using human cells," Bucher said.

Board member Miguel Fernandez, M.D., of University of Texas Health Science Center, served as a reviewer and discussant for the draft concept on light at night. He said health care workers are an important target audience for this kind of study. (Photo courtesy of Steve McCaw)

Systematic review

Andrew Rooney, Ph.D., deputy director of OHAT, presented on the implementation of systematic review and evidence integration for literature based health assessments. Rooney focused his attention on some areas that have received the most input and questions during public comment periods and webinars recently hosted by NTP, including study quality and risk of bias. He discussed how NTP planned to approach these topics and how the public comments would inform these issues moving forward.

OHAT Director Kristina Thayer, Ph.D., then presented next steps for the systematic review process. "We expect to complete our case studies during the next calendar year. These will help us better assess the performance of our methodology and fine tune our processes," Thayer said.

Given the public interest, Thayer said, NTP is helping support the development of a free software tool that will facilitate harmonization of information collected on studies included in systematic reviews. "We're pretty excited about what this tool will do," Thayer said. Beta testing begins this summer.

David Dorman, D.V.M., Ph.D., of North Carolina State University, provided scientific advice on how to address mechanisms of action in reports and processes. (Photo courtesy of Steve McCaw)

McDiarmid, left, seemed right at home taking on her new role as BSC chair, shown with Mary Wolfe, Ph.D., director of the NTP Office of Liaison, Policy, and Review. (Photo courtesy of Steve McCaw)

Draft concept

The final topic discussed at the meeting was something rather new for NTP — getting input on how to define an exposure, light at night, that has been nominated for study.

"We want to define this so it is meaningful to public health," said NTP Associate Director John Bucher, Ph.D. Lunn walked the BSC through the draft concept, shift work at night, light at night, and circadian disruption. She pointed out that those nominating the exposure were concerned that light at night may be a cause of breast cancer among women, and noted that the International Agency for Research on Cancer has classified shiftwork, involving circadian disruption, as a probable carcinogen.

The Board concluded that NTP was in the best position to address this very broad, important topic, but urged it to proceed with caution, consult technical experts, and try to narrow its focus.

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

Thayer, who leads OHAT, talked about next steps for systematic review. (Photo courtesy of Steve McCaw)

OHAT deputy director Rooney addressed some of the ways NTP is revising its systematic review process based on public input. (Photo courtesy of Steve McCaw)

Bucher encouraged the board to share their thoughts about how the NTP should be moving forward. (Photo courtesy of Steve McCaw)

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Early-life traffic-related air pollution exposure linked to hyperactivity

By Keith Herrell

Early-life exposure to traffic-related air pollution was significantly associated with higher hyperactivity scores at age 7, according to new research from the University of Cincinnati (UC) and Cincinnati Children's Hospital Medical Center. The findings appear in an NIEHS-funded study published in the June issue of Environmental Health Perspectives.

Newman was also the corresponding author on the study. (Photo courtesy of UC)

The research was conducted by faculty members from the UC College of Medicine Department of Environmental Health in collaboration with Cincinnati Children's. Nicholas Newman, D.O., director of the Pediatric Environmental Health and Lead Clinic at Cincinnati Children's and an assistant professor of pediatrics at UC, was the study's first author.

"There is increasing concern about the potential effects of traffic-related air pollution on the developing brain," Newman said. "This impact is not fully understood, due to limited epidemiological studies.

"To our knowledge, this is the largest prospective cohort with the longest follow-up investigating early life exposure to traffic-related air pollution and neurobehavioral outcomes at school age." Scientists believe that early life exposures to a variety of toxic substances are important in the development of problems later in life.

Implications of exposure in the first year of life

Newman and his colleagues collected data on traffic-related air pollution (TRAP) from the Cincinnati Childhood Allergy and Air Pollution Study (CCAAPS), a long-term epidemiological study examining the effects of traffic particulates on childhood respiratory health and allergy development. Funded by NIEHS, CCAAPS is led by Grace LeMasters, Ph.D., of the UC environmental health department. Study participants — newborns in the Cincinnati metropolitan area from 2001 through 2003 — were chosen based on family history and their residence being either near or far from a major highway or bus route.

LeMasters has served as lead researcher on other NIEHS-funded grants. She was also a member of the NIEHS National Advisory Environmental Health Sciences Council. (Photo courtesy of Steve McCaw)

Children were followed from infancy to age 7, when parents completed the Behavioral Assessment System for Children, 2nd Edition, assessing attention deficit hyperactivity disorder and related symptoms, including attention problems, aggression, conduct problems, and atypical behavior. Of the 762 children initially enrolled in the study, 576 were included in the final analysis at 7 years of age.

Results showed that children who were exposed to the highest third amount of TRAP, during the first year of life, were more likely to have hyperactivity scores in the at risk range when they were 7 years old. The at risk range for hyperactivity in children means that they need to be monitored carefully because they are at risk for developing clinically important symptoms.

"Several biological mechanisms could explain the association between hyperactive behaviors and traffic-related air pollution," Newman says, including narrowed blood vessels in the body and toxicity in the brain's frontal cortex.

Newman notes that the higher air pollution exposure was associated with a significant increase in hyperactivity only among those children whose mothers had greater than a high school education. Mothers with higher education may expect higher achievement, he said, affecting the parental report of behavioral concerns.

Potential for primary prevention

"The observed association between traffic-related air pollution and hyperactivity may have far-reaching implications for public health," Newman said, noting that studies have shown that approximately 11 percent of the U.S. population lives within 100 meters of a four-lane highway and that 40 percent of children attend school within 400 meters of a major highway.

"Traffic-related air pollution is one of many factors associated with changes in neurodevelopment, but it is one that is potentially preventable."

In addition to support by NIEHS, funding was also provided by the National Institute for Occupational Safety and Health.

Citation: Newman NC, Ryan P, Lemasters G, Levin L, Bernstein D, Hershey GK, Lockey JE, Villareal M, Reponen T, Grinshpun S, Sucharew H, Dietrich KN. 2013. Traffic-related air pollution exposure in the first year of life and behavioral scores at 7 years of age. Environ Health Perspect 121(6):731-736.

(Keith Herrell is a public information officer with the UC Academic Health Center Public Relations and Communications publication healthNEWS, where this story originally appeared to coincide with online publication May 21.)

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Study links mitochondrial variation with air pollution exposure response

By Eddy Ball

In what the authors believe is the first epidemiological evidence of its kind, a new study links mitochondrial DNA with susceptibility to air pollution. Published May 23 in the journal PLOS ONE, the study examined associations between elderly individuals' inflammatory response to components of traffic-related air pollution and their mitochondrial DNA haplogroup — the unique pattern of single-nucleotide polymorphisms (SNPs) that make up their cells' energy-production DNA, which is independent of the nuclear DNA that encodes most of the rest of the genome.

Wittkopp is an NIEHS-funded fellow in the UCI Medical Scientist Training Program. She was honored with the 2013 Women in Medicine Student Scholarship and selected as the TEDxUCIrvine Salon Speaker in February. (Photo courtesy of Sharine Wittkopp)

The research team was led by two NIEHS-funded scientists, M.D./Ph.D. fellow and first author Sharine Wittkopp, and professor and lead author Ralph Delfino, M.D., Ph.D., from the University of California, Irvine (UCI). They found that people with haplogroup H, in contrast to those with haplogroup U, showed adverse modification of the effects of air pollution on the production of inflammatory cytokines, specifically interleukin 6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha). A number of scientific studies have associated IL-6 and TNF-alpha with the initiation and progression of cardiovascular and other diseases.

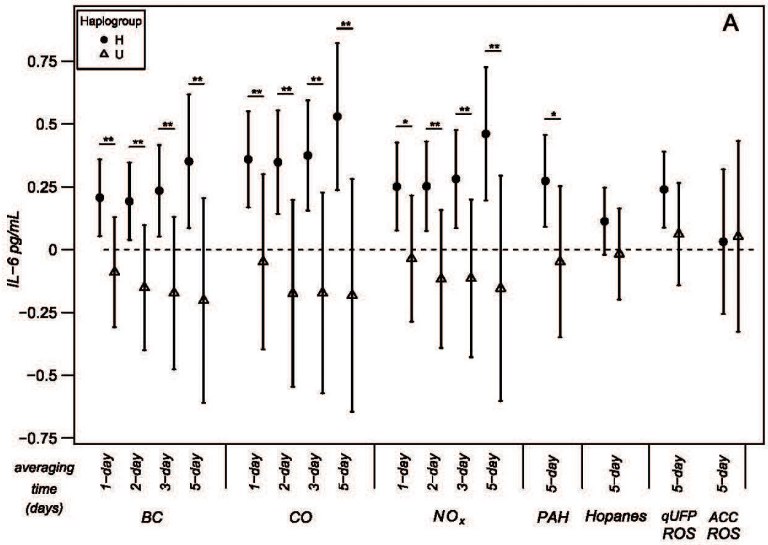
Delfino is a professor and vice-chair for graduate education and research in the Department of Epidemiology at the UCI School of Medicine. (Photo courtesy of UCI)

"This finding is relevant to advancing the field of personalized medicine," the team concluded, "since such studies indicate there is potential value in tailoring interventions based on mitochondrial haplogroup. For example, antioxidant treatment in those with greater intrinsic oxidative stress may help ameliorate the proinflammatory effects of environmental pro-oxidant chemicals, such as those in traffic-related air pollution."

Epidemiology, biomarker measurement, genotyping, and exposure analysis

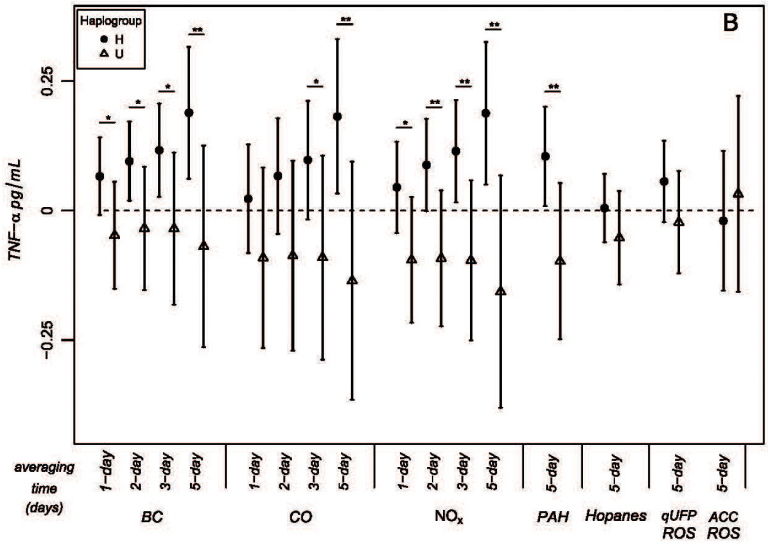
The team began with an established cohort of 60 elderly residents with coronary artery disease, at four retirement communities in the Los Angeles air basin, where air pollution levels are generally higher than in other urban areas in the U.S. To control for exposure, only residents with no outside employment were accepted. Genotyping resulted in identifying 27 subjects belonging to haplogroup H, and nine to haplogroup U, while the remainder had mitochondria from other haplogroups.

Biomarkers measured include IL-6, TNF-alpha, C-reactive protein, IL-6 soluble receptor, and TNF-alpha soluble receptor II. Air pollutants included nitrogen oxides (NOx), carbon monoxide (CO), black carbon, (BC), and other markers of fossil fuel combustion, and three sizes of particulate matter (PM). Over the 47-week period, the team also analyzed PM for polycyclic aromatic hydrocarbons (PAH); hopanes, which are found in lubricant oils of diesel and gasoline vehicles; and *in vitro* oxidative potential (ROS) of aqueous particle extracts.



Outcomes

For many of the measured traffic-related air pollution components, the team found elevated levels of IL-6 and TNF-alpha in participants with haplogroup H, and in most cases the differences between responses by people in the different haplogroups were dramatic (see graphs).



Published in PLOS ONE as part of the study, these graphs show marked differences in the inflammatory responses of H and U haplogroups to traffic-related air pollution exposure. (Graphs courtesy of Sharine Wittkopp)

As earlier research has found in relation to epilepsy, Parkinson's, and other diseases, people in this study with the mitochondrial DNA haplogroup U enjoyed greater protection from traffic pollution-related cardiovascular disease, because of their lower mitochondrial production of ROS. Exposures among those with haplogroup H were associated with greater increases in systemic inflammation and, thus, susceptibility to the adverse effects of air pollution.

"These results support the hypothesis that relatively small differences in mitochondrial coupling efficiency, which alter the cellular oxidative burden, may alter responses to exogenous inducers of oxidative stress, such as traffic-related air pollution," the researchers concluded. "This potentially important genetic risk factor has not been previously assessed in environmental epidemiological studies."

Citation: Wittkopp S, Staimer N, Tjoa T, Gillen D, Daher N, Shafer M, Schauer JJ, Sioutas C, Delfino RJ. 2013. Mitochondrial genetic background modifies the relationship between traffic-related air pollution exposure and systemic biomarkers of inflammation. PLoS One 8(5):e64444.

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Researchers solve questions about phenobarbital action in the liver

By Heather Franco

A new study led by Masahiko Negishi, Ph.D., head of the NIEHS Pharmacogenetics Group, was recognized by the Faculty of 1000 (F1000) for its contribution to the fields of phenobarbital and epidermal growth factor research. The paper appeared in the May 7 issue of the journal Science Signaling.

The study by first author Shingo Mutoh, Ph.D., a postdoctoral fellow with the group, and colleagues, addressed an issue that has plagued the research community of drug metabolism and disposition for decades, by determining the mechanism by which phenobarbital activates the constitutive active androstane receptor (CAR). They found that phenobarbital directly binds to the epidermal growth factor receptor (EGFR), blocking a signaling cascade that normally prevents the dephosphorylation and activation of CAR.

This article is the first from the Negishi lab to be recognized by F1000, which consists of more than 10,000 faculty and associate faculty members who highlight recent scientific publications of importance to their fields of research. As Linda Pike, Ph.D., notes in her recommendation of the paper, "This manuscript is interesting from two perspectives." In addition to resolving the mechanism by which phenobarbital activates CAR, the study provides new evidence for a drug interacting with EGFR to inhibit its action (see text box).

Findings could have broad implications for human health

The identification of a novel mechanism that explains how a drug activates a nuclear receptor opens up new avenues for discovery.

First, a number of environmental agents perform activation functions similar to those of phenobarbital. However, their mechanisms of action are unclear. It is possible that these chemicals act in a similar manner to phenobarbital, by directly binding to a kinase receptor at the cellular membrane to regulate a signaling cascade that activates a nuclear receptor.

Second, as Mutoh explained, "This mechanism may help in drug discovery, as companies that screen chemicals for their induction of drug-metabolizing enzymes can now also use EGFR activity as an additional readout of their efficacy."

Lastly, Negishi said, "These results greatly expand the field of nuclear receptor research, by demonstrating their regulation by membrane receptors." Thus, the results of this study could have broad implications for a number of human health issues associated with aberrant growth factor and nuclear receptor signaling.

Identifying a novel mechanism of phenobarbital action

Phenobarbital is a barbiturate used to treat epilepsy. As Negishi explained, "In 1963, phenobarbital was found to increase the expression of drug metabolizing enzymes in the liver and, because of this, patients developed drug resistance." He remembers this discovery well, since it occurred while he was in graduate school. Since then, the search for the phenobarbital receptor has been underway. More than fifteen years ago, Negishi's lab was the first to identify the nuclear receptor CAR as the mediator of phenobarbital action, but it turned out to not be the receptor for phenobarbital. He has sought to identify the phenobarbital receptor and to understand its mechanism of action ever since.

Continuing his pioneering work, Negishi's lab determined that phenobarbital promotes the dephosphorylation and nuclear translocation of CAR to activate gene transcription. Mutoh joined the Negishi lab in 2006, after earning his Ph.D. from the Tokyo University of Agriculture, and began to work towards understanding this mechanism further.

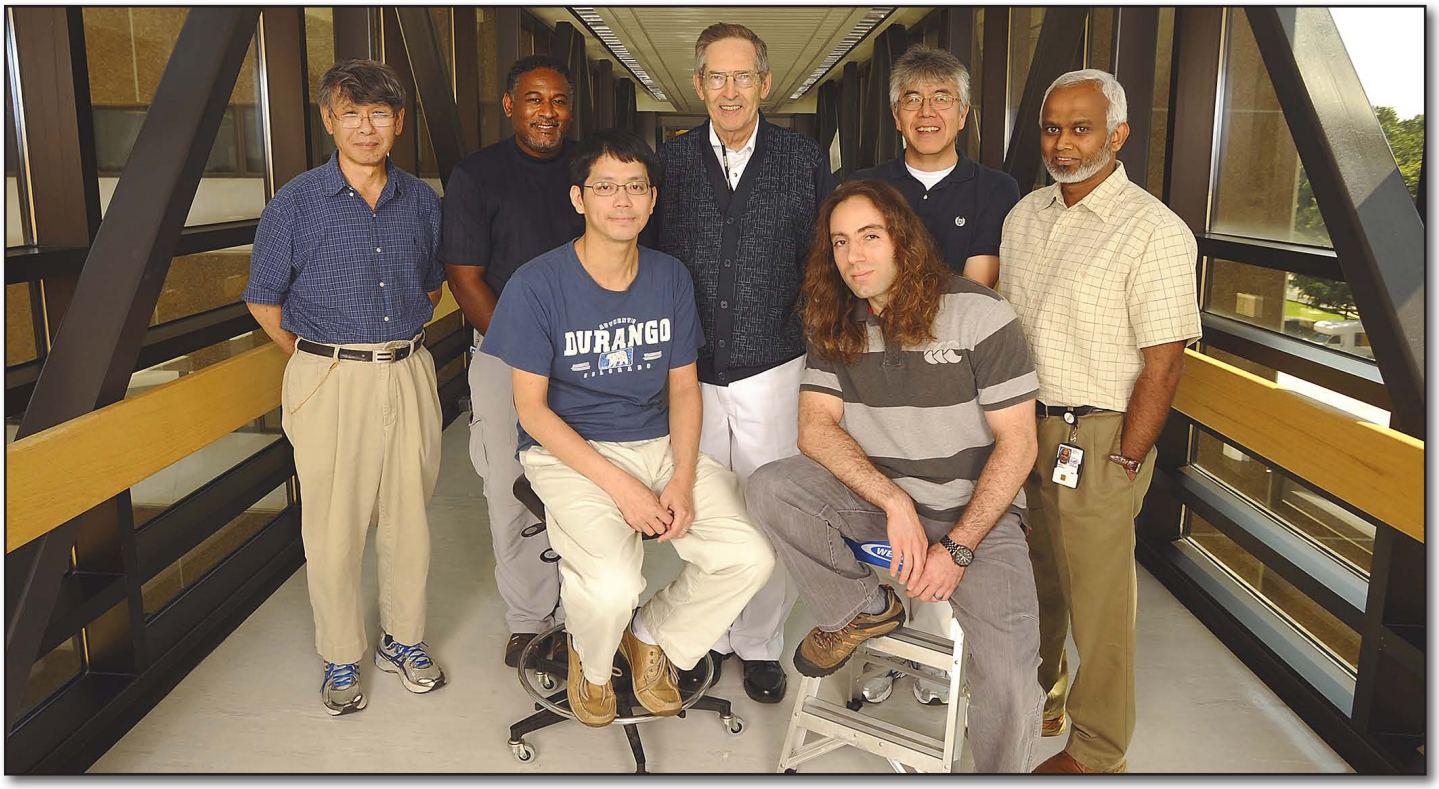
Using primary mouse hepatocytes, Mutoh observed that the EGFR ligand epidermal growth factor (EGF) prevented phenobarbital-induced CAR activation. He further demonstrated that EGF treatment prevented the association of the scaffold protein RACK1 and the protein phosphatase PP2Ac with CAR, thereby blocking its dephosphorylation and activation. Since RACK1 is a common effector in a number of signaling cascades, these findings implicated RACK1 as a hub for multiple inputs that regulate CAR actions, as well as diverse phenobarbital actions.

Closure after decades of uncertainty

These data suggested to Mutoh that phenobarbital may interact directly with EGFR, and he took two approaches to address this hypothesis. Initially, Mack Sobhany, a biologist with the group and an expert in isothermal titration calorimetry, utilized this technique to demonstrate direct binding of phenobarbital to EGFR. Simultaneously, Negishi reached out to his longtime collaborators, NIEHS lead researchers Lee Pedersen, Ph.D. and Lalith Perera, Ph.D., of the Computational Chemistry/Molecular Modeling Support Group, to model the potential binding of phenobarbital to EGFR. Their model predicts that phenobarbital binds to EGFR, overlapping with the EGF binding site, suggesting that phenobarbital may interfere with EGF binding to EGFR.

As Negishi explained, "Each result confirmed the other." These results not only resolved the half-century-old question of what is the phenobarbital receptor, by identifying EGFR, but also addressed the mechanism by which phenobarbital regulates drug metabolism in the liver.

Citation: Mutoh S, Sobhany M, Moore R, Perera L, Pedersen L, Sueyoshi T, Negishi M. 2013. Phenobarbital indirectly activates the constitutive active androstane receptor (CAR) by inhibition of epidermal growth factor receptor signaling. Sci Signal 6 (274):ra31.(Heather Franco, Ph.D. is an Intramural Research Training Award postdoctoral fellow in the NIEHS Reproductive Developmental Biology Group.)



The study grew out of collaboration between researchers in the Laboratory of Reproductive and Developmental Biology, and the Laboratory of Structural Biology. Shown, from left, are Negishi, Rick Moore, Mutoh, Pedersen, Sobhany, Tatsuya Sueyoshi, Ph.D., and Perera. (Photo courtesy of Steve McCaw)

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New approach creates red blood cells, platelets *in vitro*

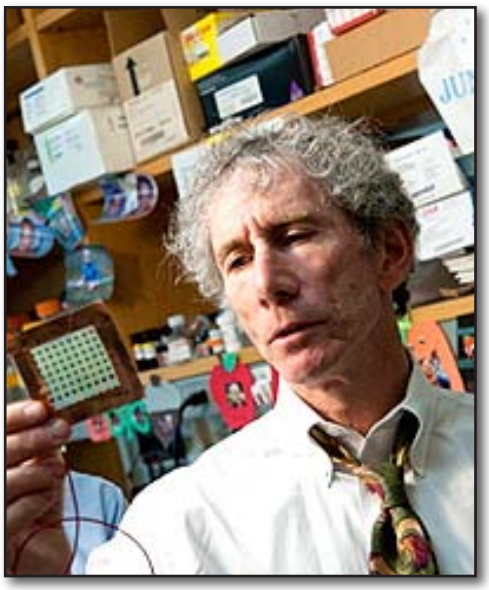
By Marisa Naujokas

An unlimited number of red blood cells and platelets can be generated from induced pluripotent stem (iPS) cells *in vitro*, according to a recent study out of the Boston University School of Medicine (BUSM) and School of Public Health (BUSPH), funded in part by NIEHS. This method could provide red blood cells and platelets for research and therapies, while also reducing the need for blood donations to treat patients requiring blood transfusions.

Murphy is head of a basic science and translational laboratory in the hematology and oncology section at BUSM. (Photo courtesy of Vernon Doucette)

George Murphy, Ph.D., assistant professor of medicine and co-director of the Center for Regenerative Medicine at BUSM, led the study, in collaboration with researcher David Sherr, Ph.D., professor of environmental health at BUSPH and deputy director of the NIEHS-funded Boston University Superfund Research Program. The report was published online May 30 in the journal Blood.

"This finding has enabled us to overcome a major hurdle in terms of being able to produce enough of these cells to have a potential therapeutic impact both in the lab and, down the line, in patients," said Murphy.



Sherr is also director of the Immunology Training Program, and a member of the Hematology/Oncology Training Program, the Cancer Center, and the Amyloid Treatment and Research Center at Boston University. (Photo courtesy of Kalman Zabarsky)

From stem cells to red blood cells and platelets

Previous research has shown that iPS cells can be generated by reprogramming normal adult cells, such as skin or blood cells, into a more primitive stem cell state. From this stem cell state, they can then be pushed to differentiate into other cell types, such as hematopoietic cells, which are blood cell precursors.

In this study, researchers used growth factors and a patented technology to push iPS cells to differentiate into red blood cells and platelets. A new twist in their investigation revealed one mechanism that contributes to this differentiation — signaling through the aryl hydrocarbon receptor (AhR). The AhR pathway is involved in cellular proliferation and differentiation in many cell types, including tumor cells. Some environmental toxins, such as dioxins, can stimulate the AhR, and are linked to a number of adverse health effects, including cancer. In this study, modulating the AhR receptor in the iPS cells drove an unprecedented rapid increase in the number of new red blood cells and platelets *in vitro*. These results open the door to the possibility of generating large numbers of cells for research and therapeutic purposes.

Implications for therapeutics and blood supplies

When created from a patient's own cells, these iPS-derived blood cells are not viewed by the immune system as foreign material and may be used in therapies without concern for an immune response against the cells. They, therefore, have the potential to be a powerful tool in therapy for blood-related illnesses, such as malaria and blood-clotting disorders. This method of generating cells could also help offset blood supply shortages. Meeting the demand for blood transfusions can be challenging, particularly in the wake of natural or man-made disasters. A recent study out of Germany predicts that increasing demands for blood products could put a significant strain on blood supplies by 2050.

"Patient-specific red blood cells and platelets derived from iPS cells, which would solve problems related to immunogenicity and contamination, could potentially be used therapeutically, and decrease the anticipated shortage and the need for blood donations," added Murphy.

Citation: Smith BW, Rozelle SS, Leung A, Ubellacker J, Parks A, Nah SK, French D, Gadue P, Monti S, Chui DH, Steinberg MH, Frelinger AL, Michelson AD, Theberge R, McComb ME, Costello CE, Kotton DN, Mostoslavsky G, Sherr DH, Murphy GJ. 2013. The aryl hydrocarbon receptor directs hematopoietic progenitor cell expansion and differentiation. Blood; doi:10.1182/blood-2012-11-466722 [Online 30 May 2013].

(Marisa Naujokas, Ph.D., is a research and communication specialist for MDB Inc., a contractor for the NIEHS Superfund Research Program and Division of Extramural Research and Training.)

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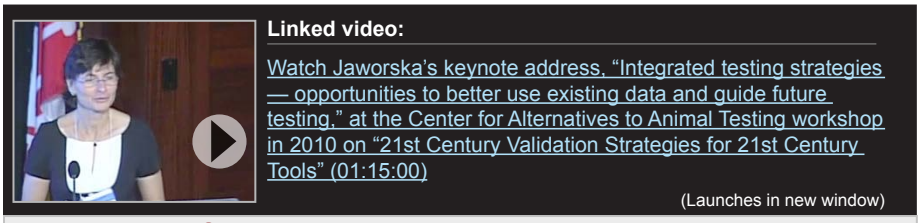
Industry scientist discusses statistical approach to safety testing

By Cathy Sprankle and Tom Burns

Manufacturers test cosmetics, household cleaners, and other chemical products before marketing, to identify any hazards they might present. One of those hazards is skin sensitization, or the potential for a product to cause an allergic skin reaction. The National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) is studying new methods to test substances for skin sensitization hazards, and recently hosted a visit from a leading industry scientist to collaborate on development of a promising new testing approach.

Jaworska is recognized as a leading authority on developing the next generation of adaptive, integrated testing strategies for skin sensitization. (Photo courtesy of Joanna Jaworska)

Joanna Jaworska, Ph.D., a principal scientist with Procter and Gamble in Brussels, Belgium, visited NIEHS May 20–21. While at NIEHS, Jaworska presented a seminar titled "Bayesian Integrated Testing Strategy to Assess Skin Sensitization Potency: From Theory to Practice," and met with NICEATM and other NTP scientists to work on creating an integrated testing strategy to identify potential skin sensitizers using non-animal test methods.



Preventing allergic contact dermatitis

Regulatory agencies around the world require testing to identify substances that may cause allergic skin reactions. Repeated exposure to these substances can cause allergic contact dermatitis (ACD), a skin condition characterized by redness, swelling, blistering, and itching. Poison ivy is a well-known cause of ACD, but chemicals that are used in consumer products, such as formaldehyde and nickel, can also cause the condition. ACD is hard to treat, so it is important to identify and properly label substances that may cause it. With proper labeling, people handling these substances have the information they need to prevent exposure.

Traditional testing methods to identify substances that cause ACD use animals, but concerns about testing efficiency and animal welfare are driving efforts to replace traditional testing methods with non-animal methods. In practice, it usually takes several non-animal tests to provide the same level of information as a single animal test.

Moving toward alternative testing

The integrated testing strategy developed by Jaworska and colleagues at Procter and Gamble provides an approach for analyzing information from non-animal tests and other information about a test substance, such as chemical structure and solubility. The analysis considers all the available relevant information about a substance and produces a numerical probability that the substance is a sensitizer. This probability could potentially be used to make decisions about whether substances require hazard labeling, without requiring animal testing.

The software used by Procter and Gamble for these analyses is patented, so Jaworska and the NTP scientists are collaborating to develop similar tools using free, publicly available software, to make the integrated testing strategy approach more widely available. "If our collaboration is successful, people and organizations worldwide will be able to use this approach for identifying potential sensitizers," commented NTP senior toxicologist Warren Casey, Ph.D., acting director of NICEATM. "It's an example of how international cooperation can support the effort towards eliminating animal testing in this area."

(Cathy Sprankle and Tom Burns are employees of ILS Inc., support contractor for NICEATM. Sprankle is senior communications specialist and Burns is a senior project coordinator/technical writer.)

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Synergistic gene-environment interactions increase schizophrenia risk

By Kristen Ryan

Using a novel genetically engineered mouse model, expressing a mutated form of the human disrupted in schizophrenia 1 (DISC1) gene, a risk factor for major psychiatric disorders, NIEHS-funded researchers investigated gene-environment interactions (GEI) that could act synergistically to contribute to mental illness.

Published May 28 in the journal Schizophrenia Bulletin, the new study demonstrated that mice with mutated DISC1 (mDISC1) exposed to lead (Pb2+) prenatally and throughout early life exhibited several

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

neurobehavioral and neuroanatomical abnormalities that reflect human attributes of schizophrenia. Behavioral tests in these mice resulted in a sex-dependent increase in hyperactivity, alone and after treatment with psychostimulants.

The mice also had a mild impairment in their ability to adapt and suppress a startle response to loud noise, pointing to difficulties with attention and sensory information processing. Furthermore, magnetic resonance imaging (MRI) of these mice revealed enlarged lateral ventricles, or empty spaces filled with cerebrospinal fluid, in their brains. These findings were specific to lead-exposed mDISC1 mice, and were not observed in mutant mice on a control diet, or in normal DISC1 mice with or without lead exposure.

Lead senior author Tomas Guilarte, Ph.D., an NIEHS-funded scientist and chair of the Department of Environmental Health Sciences at Columbia University Mailman School of Public Health, collaborated with first author Bagrat Abazyan, M.D., senior co-author Mikhail Pletnikov, M.D., Ph.D., and colleagues at Johns Hopkins University School of Medicine, to conduct this research study. The authors, who are well-established neuroscientists, wrote, "Our study is the first to use a relevant genetic mutation in combination with an environmental toxin implicated in schizophrenia in humans."

These findings have already been highlighted in several online reports, and the study continues to attract interest.

Extrapolating from gene-environment interactions in a mouse model

This research project was based on fundamental scientific premises generated by previous mechanistic and epidemiological studies that the authors reviewed.

- The glutamatergic hypothesis of schizophrenia, which implies a causal link between a decrease or hypoactivity of the N-methyl-d-aspartate receptor (NMDAR), located throughout the brain for control of synaptic plasticity and memory, and schizophrenia and other psychiatric disorders.
- The association of prenatal lead exposure with adult onset schizophrenia, based on its inhibitory action on NMDAR function.
- The involvement of GEI in schizophrenia and other mental disorders.

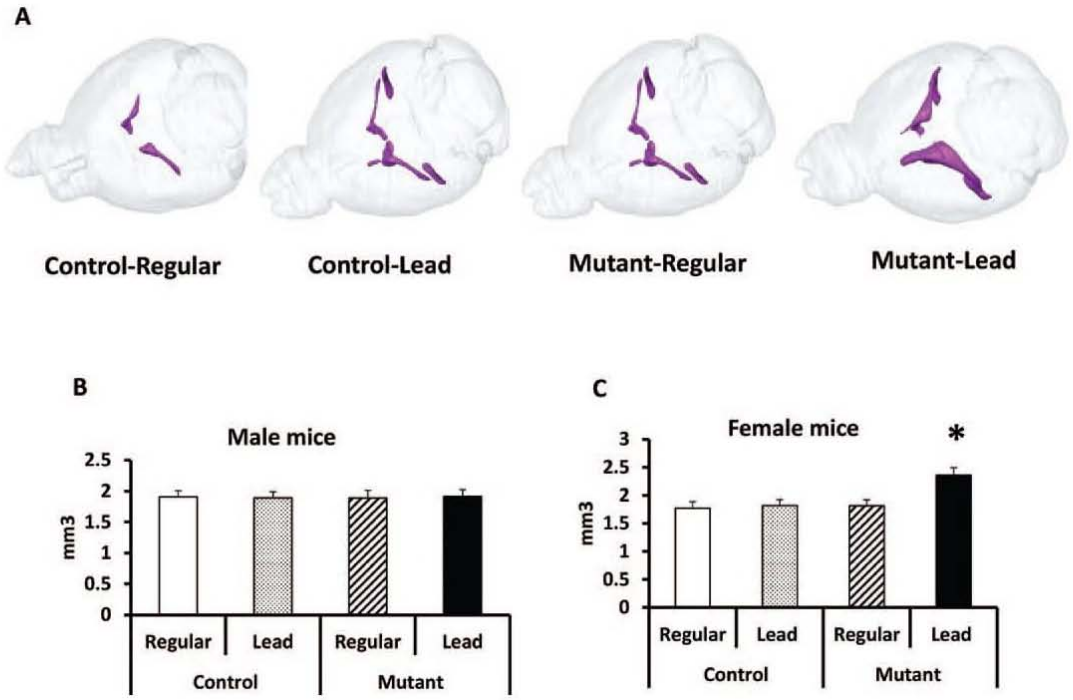
The GEI hypothesis is gaining attention and support, as the search continues for mutations in genes that could make individuals more or less susceptible to chemicals in the everyday environment. Earlier studies found the mutant form of DISC1 to be one those genes, and lead to be one of those chemicals, that affect NMDAR function.

According to the researchers, this finding opens the door to possible combinations of gene-environment interactions that could contribute to the pathophysiology of numerous complex diseases. As Guilarte explained in an interview for a Columbia University press release, "We're just scratching the surface. We used lead in this study, but there are other environmental toxins that disrupt the function of NMDAR. Similarly, any number of genes could be in play."

Notably, NIEHS and the National Toxicology Program are investigating the toxicity of various other chemical classes and mixtures, some of which are suspected to be risk factors for neurological disorders. Two examples are polycyclic aromatic hydrocarbons (PAHs) and flame retardants, both of which are widespread in the environment and have observed health effects. Ongoing and future research in genetically engineered rodent models, perhaps modeled after this study's model, could provide greater insight into novel gene-environment interactions, and help explain some of the complex pathophysiology of mental illness and various other disorders.

Citation: Abazyan B, Dziedzic J, Hua K, Abazyan S, Yang C, Mori S, Pletnikov MV, Guilarte TR. 2013. Chronic exposure of mutant DISC1 mice to lead produces sex-dependent abnormalities consistent with schizophrenia and related mental disorders: a gene-environment interaction study. Schizophr Bull; doi: 10.1093/schbul/sbt071 [Online 28 May 2013].

(Kristen Ryan, Ph.D., is an Intramural Research Training Award Fellow in the NTP Toxicology Branch.)



*In addition to molecular and behavioral studies, the team performed MRI studies of brain volume effects of gene-environment interaction. (A) Representative MRI 3D images for the control-regular, control-lead, mutant-regular, and mutant-lead groups of female mice, with the lateral ventricles are outlined in purple. (B) Male mice showed no genotype-related or diet-related alterations in lateral ventricle volume. (C) mDISC1 female mice exposed to Pb2+ had a marked increase in lateral ventricle volume compared with all other groups; *P = .05 for the genotype-diet interaction; n = 5 mice per group. (Photo courtesy of Tomas Guilarte)*

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Suffering from skin allergies? TRPA1 may be the key to skin relief

By Sheila Yong

As one of the first recipients of an Outstanding New Environmental Scientist (ONES) grant award, when they were first offered by NIEHS in 2006, Sven-Eric Jordt, Ph.D., has come a long way in studying how certain airborne pollutants interact with sensory nerve cells to cause eye, nose, and throat irritation. His research, thus far, has yielded exciting findings on the role of the transient receptor potential (TRP) ion channel TRPA1 in driving asthmatic airway inflammation, as well as hypersensitivity caused by a wide range of irritants (see story).

The associate professor in the Department of Pharmacology at Yale University has now taken this research a step further, to investigate how TRPA1 may also be involved in triggering the inflammatory responses in allergic contact dermatitis (ACD). Funded in part by NIEHS, the study was published in the May 30 online edition of The FASEB Journal.

What do ACD and asthma have in common?

ACD is a skin condition that often presents with red rash and blisters, as well as itching and burning skin. "ACD and asthma share similar etiologies, in that they are both triggered by initial exposures to allergens and produce a local Th2-driven inflammatory response at the site of challenge," Jordt explained. "We began our study on ACD in 2009, while completing our experiments on the asthma model, because we were curious to find out whether the sensory neurons in the skin and their TRP channels would also be involved in maintaining inflammation in ACD."

Jordt is grateful for the support he receives from NIEHS. "Funding from NIEHS has continued to allow my team to discover novel and unexpected findings, which may lead to new approaches for treating and preventing ACD." (Photo courtesy of Steve McCaw)

ACD is triggered by small reactive chemicals called haptens, which react with proteins in the skin to form strongly immunogenic epitopes, parts of an antigen molecule that sensitize the immune system to respond to subsequent challenges. Haptens are present in a variety of natural, industrial, and consumer products, including detergents, fragrances, and food additives. The most commonly encountered hapten is urushiol, which is produced by poison ivy, oak, and sumac. ACD resulting from urushiol exposure affects more than 10 million patients a year, in the United States alone.

Jordt's team used both urushiol and oxazolone as their model haptens in this study. They showed that while wild-type mice exhibited skin inflammation upon allergen challenge, the response in TRPA1-deficient mice was significantly reduced. Naturally, the use of HC-030031, a well-established TRPA1 antagonist, diminished the skin inflammation in wild-type mice. Using antibody-based and immunofluorescence-based techniques, the researchers also detected an increase in levels of inflammatory cytokines and skin infiltration by T cells at ACD-affected sites, both of which could be subdued by HC-030031. On the other hand, mice lacking TRPV1, a TRP family member that is structurally related to TRPA1, suffered the same extent of skin irritation as the wild-type mice, indicating that TRPV1 is not involved in the inflammatory responses in ACD.

Jordt also described a fascinating phenomenon known as the atopic march, where patients suffering from ACD, particularly atopic dermatitis, often develop asthma. "It is speculated that the inflammatory signals from the skin eventually trigger sensitization of the airways, leading to asthma attacks in these patients," he noted. Whether or not TRPA1 is the missing link between ACD and asthma remains to be determined.

Citation: Liu B, Escalera J, Balakrishna S, Fan L, Caceres AI, Robinson E, Sui A, McKay MC, McAlexander MA, Herrick CA, Jordt SE. TRPA1 controls inflammation and pruritogen responses in allergic contact dermatitis. FASEB J; doi:10.1096/fj.13-229948 [Online 30 May 2013].

(Sheila Yong, Ph.D., is a visiting fellow in the NIEHS Laboratory of Signal Transduction.)

Overcoming the hurdle in treating ACD

One major complication of ACD is pruritus, more commonly known as itching. However, since ACD-associated pruritus is resistant to antihistamines, there are few treatment options for chronic sufferers whose quality of life is severely impacted. "We decided that our ACD mouse model is ideal for studying histamine-independent pruritus, since TRPV1 has been reported to induce histamine-mediated pruritus, but has no effect on the inflammatory responses in ACD," Jordt commented.

To this end, his study revealed TRPA1 as a critical mediator of histamine-independent itching, since TRPA1-deficient mice exhibited reduced ACD-associated scratching behavior compared to wild-type and TRPV1-deficient mice. More importantly, his team also discovered several downstream signaling pathways crucial for histamine-independent pruritus that are facilitated by several peptide mediators. These include Substance P, a neuropeptide expressed in the inflamed skin; endothelin-1, a peptide secreted by cells lining the interior surface of blood vessels; and neurotransmitter serotonin.

Jordt hopes that his findings will advance the field of ACD treatment. "In addition to TRPA1, these downstream pathways are also suitable drug targets for novel anti-itch medications that are effective for treating ACD," he concluded.

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Crystallography meeting showcases advances in biomedical research

By Raj Gosavi

Structural biologists from NIEHS were on hand as the annual Mid-Atlantic Macromolecular Crystallography (MAMC) Meeting marked its 43rd year May 30-June 1 at Duke University.

Starting in 1970 as a small group gathering at a professor's home in Charlottesville, Va., the meeting has flourished over the years. Head of the organizing committee and chair of Duke Department of Biochemistry Richard Brennan, Ph.D., said that this year's meeting attracted a record number of attendees — more than 180 — traveling from as far away as Connecticut.

As one of the powerful structural biology techniques, crystallography offers a unique perspective into the world of proteins, enzymes, and nucleic acids (see text box). The annual MAMC meeting provides attendees with an opportunity to share the latest developments in structural biology, and to exchange the most current techniques in the field of macromolecular crystallography.

As the meeting's keynote speaker, Los Alamos National Laboratory structural genomics researcher Thomas Terwilliger, Ph.D., said afterwards, "The Mid-Atlantic Macromolecular Crystallography

Terwilliger presented improvements to crystallographic modeling tools in his talk, "Molecular replacement and model-building using distant homology models as template." He agreed that there is extensive interaction between researchers developing software and algorithms for structure determination, and structural biologists who use that software. (Photo courtesy of Steve McCaw)

Meeting was a wonderful success. It was a great opportunity to see exciting structural biology results, and new methods for X-ray crystal structure determination and analysis."

Brennan provided opening remarks and led the organizing committee for a very successful MAMC meeting. (Photo courtesy of Steve McCaw)

A grand group meeting

The posters and talks provided three-dimensional snapshots of macromolecules involved in cell signaling, cellular disruption and defense, nucleic acid biology, and cell division. One of the speakers, Bret Freudenthal, Ph.D., a postdoctoral fellow in the NIEHS Laboratory of Structural Biology (LSB) DNA Repair and Nucleic Acid Enzymology Group headed by Samuel Wilson, M.D., utilized time-resolved crystallography to capture an additional metal binding site transiently formed in the polymerase active site following catalysis, which has been undetectable using other approaches.

The meeting had a perfect mix of scientists from universities, research institutes, and industry. One of the attendees, NIEHS visiting fellow Sara Andres, Ph.D., of the LSB Genome Stability Structural Biology Group headed by Scott Williams, Ph.D., remarked, "Most of the speakers are graduate students and postdoctoral fellows, which provides a valuable career development opportunity." Other NIEHS attendees, including LSB biologist Andrea Moon, remarked on the camaraderie among attendees that created a comfortable setting for interpersonal interaction.

Technological advances in the field of crystallography

Among the sponsors for the meetings were vendors who exhibited improved tools for crystallographers. Vendors attending this meeting each year benefit from interactions with the scientific community, as much as the scientists do from the representatives. Mike Murray, Ph.D., currently with Rigaku and formerly a member of the NIEHS Laboratory of Molecular Genetics group headed by Thomas Kunkel, Ph.D., said, "This meeting is one of the best crystallography meetings I get to attend. Knowing the cutting-edge science being presented helps us push the developments [in supplies and equipment] even further."

Program developers and users

The final step in obtaining a crystal structure of a macromolecule consists of utilizing computer programs available for the purpose. Presentations and workshops from the program developers provide opportunities to learn, for both beginners and advanced users. This cross talk between the users and developers makes the programs more efficient and accommodating.

The crystallography community in the Research Triangle Park, N.C., area, including scientists at NIEHS, continues to enjoy outstanding success in the field. The number of scientists utilizing crystallography in their work is constantly growing and currently includes NIEHS researchers with interests in structural biology, molecular genetics, signal transduction, reproductive and developmental toxicology, and neurobiology. The crystallography facility at NIEHS continues to expand and become more efficient, as it provides core support for the growing number of users.

(Raj Gosavi, Ph.D., is a research fellow in the NIEHS Structure and Function Research Group.)

Freudenthal was one of several speakers and participants from NIEHS at the meeting. (Photo courtesy of Steve McCaw)

Andres said that the selection of speakers was excellent, providing useful career development opportunities for trainees and students. (Photo courtesy of Steve McCaw)

Duke University professor Jane Richardson, Ph.D., was also on hand for the meeting. She and her research group have contributed immensely in the development of software for protein crystallography. (Photo courtesy of Steve McCaw)

Moon said she found the workshops offered by program developers very helpful and relevant to her work at the bench. (Photo courtesy of Steve McCaw)

The power of macromolecular crystallography

Macromolecular X-ray crystallography is a technique used to determine the atomic resolution structures of macromolecules, such as proteins and enzymes, nucleic acids, ribosomes, and viruses. The diffraction of X-rays from macromolecules in a crystal is used to obtain information in the form of electron density around the atoms in a molecule. The chemical structure is then determined by fitting a model to the electron density.

While much can be learned from amino acid or nucleic acid sequences, the strength of crystallography is in its ability to provide the important third dimension. Due to its powerful nature, biochemists have been applying crystallography to address questions ranging in size from small chemicals to large intermolecular protein interactions.

In the 100 years following the discovery of X-ray diffraction, X-ray crystallography has found applications in many areas, including biology and biotechnology. Starting from small molecule structure determination, the interdisciplinary field progressed in the early days with research by inorganic chemists, material scientists, and mineralogists. Physicists were instrumental in the birth of X-ray crystallography, and even now crystallography continues to contribute to, and gain from, the efforts of physicists.

The application of crystallography to macromolecules has enabled its valuable contributions to biomedical research. Crystallography also continues to advance the environmental health sciences, by providing insights into the effect of environmental agents on human health.

The versatile nature of the X-ray crystallography is evidenced from its wide application in multiple disciplines. Because of the power and wide application, the General Assembly of the United Nations is recognizing 2014 as the International Year of Crystallography.

Risk assessment workshop features cutting-edge toxicogenomic research

By Sara Mishamandani

Scientists and regulators from around the world met to review progress in human carcinogenesis safety evaluation strategies and cancer risk assessment May 16-17 at the Moving Forward in Human Cancer Risk Assessment in the Genomics Era 2.0 workshop held at the OECD (Organisation for Economic Co-operation and Development) Congress Centre in Paris. The meeting was co-sponsored by NIEHS.

Auerbach (second from left) discussed integrating genomics in carcinogenicity testing during his presentation. (Photo courtesy of Rene Reijnders, Maastricht University)

Scott Auerbach, Ph.D., a molecular toxicologist with the National Toxicology Program and NIEHS-funded Superfund Research Program (SRP) grantee Ivan Rusyn, M.D., Ph.D., a professor of environmental sciences and engineering at the Gillings School of Global Public Health at the University of North Carolina at Chapel Hill, were among the speakers at the meeting. Richard Paules, Ph.D., the Molecular Genomics Core director at NIEHS, was one of the organizers of the workshop and served as session chair, roundtable discussion leader, and presenter of the meeting summary. They joined representatives of the academic and industry safety assessment communities, government regulators, and risk assessors from the U.S., European Union, and Japan.

Rusyn used his NIEHS-funded research to explain how to combine biological and chemical information to better understand human toxicity. (Photo courtesy of Rene Reijnders, Maastricht University)

"Getting regulators, toxicologists, and informaticians to talk to each other, and translate paradigms and views across knowledge domains, helps advance the goals of 21st century toxicology," said Auerbach. "One of the things you really notice at meetings like this one is that there are people with problems without solutions — regulators and toxicologists — and people with solutions without problems — informaticians — finding each other and later working together to find a solution that works across multiple domains. In many ways, the meeting was a reflection of the cross-disciplinary nature of the toxicological sciences in today's world."

Expanding the boundaries of toxicogenomics

Rusyn presented a vision for effectively integrating data to facilitate hazard characterization. He discussed how to combine gene expression data with chemical information to improve predication of drug and chemical toxicity.

The number of toxicogenomic studies that incorporate dose-response and population-based designs is on the rise, and the applicability of such data to hazard assessment is increasing. Rusyn described a user-friendly computational approach for dose-response analysis of gene expression data at the pathway level. He also

suggested that the challenge of understanding inter-individual differences in toxicity may be met through a combined analysis of toxicity phenotypes and gene expression data from genetically diverse, recombinant inbred mice.

"This meeting afforded a unique opportunity for a candid conversation with practitioners and regulators about the value of genomics in decision-making with respect to human health assessments of drugs and environmental chemicals," said Rusyn. "A real opportunity exists for moving the field of human health risk assessment into the future, by expanding the use of omics beyond heatmaps and network diagrams."

Moving cancer risk assessment forward

The driving force of the workshop was the need to improve human cancer risk assessment with better assessment approaches, assays, exposure estimates, and decision trees, so that toxicologists can ultimately use fewer animals in testing and provide more reliable information concerning human risk.

The current safety paradigm for assessing carcinogenic properties of drugs, cosmetics, industrial chemicals, and environmental exposures relies mainly on in vitro genotoxicity testing, followed by two-year rodent bioassays. This testing battery is extremely sensitive, but has low specificity. Rodent bioassays are also associated with high costs, high animal burden, and limited predictive value for human risks. Workshop participants discussed developing alternative testing strategies for carcinogenicity, with emphasis on potential contributions from omics technologies.

"As pointed out by one of the participants, there was a recognition and acknowledgement that advances in technology, that will revolutionize human cancer risk assessment, are coming, some of which are here now, and are unstoppable," said Paules.

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

Paules, center, speaks during a roundtable discussion. The panel focused on what needs to be done to achieve broad applicability of toxicology studies. Shown, left to right, are Christopher Portier, Ph.D., U.S. Centers for Disease Prevention and Control (retired); Jan Willem Van der Laan, Ph.D., Medicines Evaluation Board; Paules; Carole Yauk, Ph.D., Health Canada; and Nathalie Delrue, Ph.D., OECD. (Photo courtesy of Rene Reijnders, Maastricht University)

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This month in EHP

This month, Environmental Health Perspectives (EHP) celebrates growth in its impact factor, and highlights feature stories on sustainable farming, and the risks and rewards of nanosilver.

Food from EARTH: Sustainable Farming in Action

With its row upon row of genetically identical Cavendish banana plants stretching for acres, one might mistake EARTH University's finca bananera for a traditional banana farm. But through trial, error, and scientific research, EARTH University, funded largely by a U.S. Agency for International Development endowment, has not only created a more ecologically friendly, lower pesticide banana since the Costa Rican university was established in 1989, but also impacted the larger banana industry and nations around the world, as their alumni take sustainable agriculture initiatives and new business opportunities back to their home countries.

Nanosilver: Weighing the Risks and Rewards

The use of silver as an antimicrobial is nothing new, but recent advances in our ability to manipulate nanosilver particles, plus evidence that silver can fight antibiotic-resistant bacteria, have led to a surge of new innovations. But consensus remains elusive on subjects as essential as how nanosilver behaves in the body, how the influx of silver affects the environment, and the extent to which its use is apt to breed strains of resistant microbes.

Featured research and related news articles this month include:

- Roxarsone, Inorganic Arsenic, and Other Arsenic Species in Chicken: A U.S.-Based Market Basket Sample — Arsenical Association: Inorganic Arsenic May Accumulate in the Meat of Treated Chickens
- Solid Fuel Use for Household Cooking: Country and Regional Estimates for 1980-2010 — Filling In the Blanks on Solid Fuel Use: New Model Illustrates Trends, Highlights Needs
- Improving the Human Hazard Characterization of Chemicals: A Tox21 Update — Tox21 to Date: Steps Toward Modernizing Human Hazard Characterization
- Second-Hand Tobacco Smoke Exposure in Open and Semi-Open Settings: A Systematic Review — Outdoor Smoking Areas: Does the Science Support a Ban?

Impact factor grows

The latest impact factor for EHP is 7.26, up from last year's figure of 7.04. Calculated independently each year by Thomson-Reuters, impact factor is a measure of the frequency with which the average article published in a given scholarly journal has been cited in a particular year or period, and is often used to measure or describe the importance of a particular journal to its field. The new rankings come out in the spring, for the previous year's journals. Three years' worth of data is required to calculate a journal impact factor.

According to the 2012 Journal Citation Reports, EHP ranked third out of 205 journals in environmental sciences, and ranked second out of 157 journals in public, environmental, and occupational health.

NICEATM/EPA workshop on evaluating cardiovascular safety

By Cathy Sprankle

Pollutants and toxicants in the environment have the potential to damage cells in the heart and circulatory system. This type of toxicity, known as cardiovascular toxicity, is also a major reason for drug development failure. The environmental and medical aspects of cardiovascular toxicity make this research area interesting to a broad audience, including clinical researchers, environmental health researchers, government regulators, and drug developers.

Because of the broad current interest in cardiovascular toxicity, the National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) is joining with the U.S. Environmental Protection Agency to present a workshop addressing development of new methods to assess and predict whether substances might affect cardiovascular safety in humans. The workshop, "Translational Alternative Models and Biomarkers Predictive of Drug or Chemical Cardiovascular Risk," will be held Oct. 10-11 at NIEHS.

"Cardiovascular disease is the leading cause of death in the United States," noted Warren Casey, Ph.D., acting director of NICEATM and a co-chair of the workshop. "One objective of this workshop is to assess the role of chemical exposures in cardiovascular disease. We're also going to be examining current approaches for identifying substances likely to cause cardiovascular toxicity, and discuss how that could be done more effectively."

Determining whether a substance is likely to cause cardiovascular toxicity presents a number of challenges. Current approaches involve testing in animals and rely on observing effects, such as organ damage and blood chemistry changes, which provide evidence of toxicity, but little information about the mechanism of toxicity. The animal tests used by drug developers are much better at identifying the immediate acute effects than the damage that might occur after taking a drug for a long period of time. Because there are no standardized regulatory guidelines for cardiovascular toxicity testing, approaches for testing vary widely among industries, with testing practices among industrial chemical manufacturers being very different from those used by drug manufacturers.

The workshop will bring together scientists from these industries, academia, and regulatory agencies to consider new approaches to cardiovascular toxicity testing that will provide better safety and risk assessments while reducing or eliminating animal use. Participants will consider how to prioritize research initiatives in this area, and how to bring together data on test substances from various test methods and sources, to develop better cardiovascular toxicity hazard assessments.

More information about the workshop, including an agenda and registration information, is available on the NIEHS website at http://www.niehs.nih.gov/about/visiting/events/highlight/cardiovascular-toxicity-workshop/.

(Cathy Sprankle is a communications specialist with ILS Inc., support contractor for NICEATM.)

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Extramural papers of the month

By Nancy Lamontagne

- Teeth analysis reveals early-life dietary transitions
- Nano GO Consortium studies health effects of nanoparticles
- Prenatal BPA exposure alters brain function and behavior in mice
- Dietary nicotine associated with lower Parkinson's disease risk

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

Teeth analysis reveals early-life dietary transitions

NIEHS-supported researchers report that the ratio of barium to calcium in teeth can accurately reflect an infant's dietary transition from the introduction of mother's milk through weaning. This work identifies a new biomarker that could be useful for epidemiologic investigations of the health consequences of breastfeeding and chemical exposures during early life, and for determining developmental transitions in primates.

The researchers investigated the spatial distribution of barium and calcium in teeth, using laser ablation-inductively coupled plasma-mass spectrometry for high-resolution elemental analysis. They analyzed teeth from macaques with known diet histories, as well as teeth shed by children enrolled in the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) study, at the University of California, Berkeley, where breastfeeding and infant formula use were prospectively recorded. The analyses showed that the ratio of barium to calcium in teeth reflected the barium intake via mother's milk, and could be used to determine the exact timing of birth, when the infant was fed exclusively on mother's milk, and the weaning process. The researchers also documented the first early-life dietary transition in a juvenile Neanderthal, by applying the technique to a several-thousand-year-old Neanderthal tooth.

Citation: Austin C, Smith TM, Bradman A, Hinde K, Joannes-Boyau R, Bishop D, Hare DJ, Doble P, Eskenazi B, Arora M. 2013. Barium distributions in teeth reveal early-life dietary transitions in primates. Nature 498(7453):216-219. Story

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Nano GO Consortium studies health effects of nanoparticles

Researchers from institutions that are part of the NIEHS-funded Nano GO Consortium used mouse and rat models to examine pulmonary health effects related to titanium dioxide nanoparticles and carbon nanotube exposure. Predictable and repeatable results from multiple institutions is important for informing policies that prevent possible health risks associated with nanomaterials, and the research demonstrated that the multicenter consortium approach can provide comparable data across institutions.

Using a standard protocol across multiple labs, researchers examined three forms of titanium dioxide (TiO2) nanoparticles and three forms of multiwalled carbon nanotubes. Four laboratories evaluated lung responses to nanomaterial exposure in mice, and three labs evaluated lung responses in rats. At day one, all three types of titanium dioxide nanoparticles caused significant inflammation in mice in three of four labs. For the rat studies,

anatase nanobelts (TiO2-NB) caused inflammation in rats at day one in two of three labs, while anatase/rutile spheres (TiO2-P25) and anatase spheres (TiO2-A) had no significant effect for any of the labs. TiO2-induced inflammation in both mice and rats resolved after seven days. Original and purified multiwalled carbon nanotubes, as well as carbon nanotubes functionalized with carboxylic acid, all caused inflammation at day one in mice in three of four labs, and in rats in all three labs. The researchers say that future research using this consortium approach for toxicity testing and exposure assessment would help ensure the safe continuation and economic viability of nanotechnology.

Citation: Bonner JC, Silva RM, Taylor AJ, Brown JM, Hilderbrand SC, Castranova V, Porter D, Elder A, Oberdörster G, Harkema JR, Bramble LA, Kavanagh TJ, Botta D, Nel A, Pinkerton KE. 2013. Interlaboratory evaluation of rodent pulmonary responses to engineered nanomaterials: the NIEHS Nano GO Consortium. Environ Health Perspect; 121(6):676-682.

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Prenatal BPA exposure alters brain function and behavior in mice

A study, supported in part by NIEHS, found that low-dose prenatal bisphenol A (BPA) exposure in mice brought about lasting epigenetic changes in the brain. These changes were sex specific and associated with alterations in social and anxiety-like behavior.

The researchers exposed pregnant mice to BPA at doses of 2, 20, or 200 micrograms per kilogram a day. They then looked at how this exposure affected gene expression, DNA methylation, and social and anxiety-like behavior of the offspring. They found that these doses of BPA induced changes in expression of genes encoding estrogen receptors and estrogen-related receptors in the offspring. The BPA effects were sex-specific, dose-dependent, and brain region-specific. BPA exposure was also associated with sex-specific effects on social and anxiety-like behaviors.

The researchers say that future studies of the timing and mechanisms of the BPA-related epigenetic disruption, as well as identification of the genes and signaling pathways that may be involved, will reveal more about the mechanisms that underlie the effects of prenatal BPA exposure on the brain.

Citation: Kundakovic M, Gudsnuk K, Franks B, Madrid J, Miller RL, Perera FP, Champagne FA. 2013. Sex-specific epigenetic disruption and behavioral changes following low-dose in utero bisphenol A exposure. Proc Natl Acad Sci U S A 110(24):9956-9961.

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Dietary nicotine associated with lower Parkinson's disease risk

A study, funded by NIEHS, found that people who consumed nicotine-containing vegetables, especially peppers, had a lower risk of developing Parkinson's disease. Previous studies have consistently shown an association between tobacco product use and a lower risk of Parkinson's disease, and the new study contributes additional evidence that nicotine may be responsible for tobacco's potentially protective effect.

The researchers studied 490 people with newly diagnosed Parkinson's disease, and 644 people who were neurologically normal. They compared the consumption of peppers, tomatoes, and potatoes, which all contain

nicotine and are members of the same botanical family, *Solanaceae*, as tobacco. Parkinson's disease risk was reduced with increased frequency of consumption of these nicotine-containing vegetables (relative risk [RR]=0.81, 95 percent confidence interval [CI]=0.65-1.01 per time per day), but not for other vegetables (RR=1.00, 95 percent CI=0.92-1.10). They observed an inverse association for peppers specifically (ptrend=0.005), and noted that the trend toward a lower Parkinson's disease risk was stronger when they examined edible *Solanaceae* by nicotine concentration (ptrend=0.004), or focused on men and women who never used tobacco regularly.

The researchers caution that their findings need to be confirmed and extended through additional studies, to better understand the relationship between *Solanaceae* phytochemicals and Parkinson's disease, and whether possible dietary or pharmaceutical interventions could lessen the risk.

Citation: Nielsen SS, Franklin GM, Longstreth WT, Swanson PD, Checkoway H. 2013. Nicotine from edible Solanaceae and risk of Parkinson disease. Ann Neurol; doi:10.1002/ana.23884 [Online 9 May 2013].

(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 Aleksandra Adomas, Heather Franco, and Mallikarjuna Metukuri

- Ribonucleotides direct the mismatch repair machinery to DNA sequence errors
- Beta-arrestin-2 is major player in development of abdominal aortic aneurysm
- The role of p53 during bacterial pneumonia
- Phenobarbital directly binds to EGFR to activate CAR in the liver

Ribonucleotides direct the mismatch repair machinery to DNA sequence errors

NIEHS scientists in the DNA Replication Fidelity Group demonstrated that ribonucleotides in the nuclear genome mark new DNA strands for error correction by the mismatch repair (MMR) machinery. Since MMR defects cause genome instability and are associated with human diseases such as cancer, understanding the mechanism of MMR may eventually provide insight into the etiology of multiple human diseases.

The researchers found that the leading strand DNA polymerase has a sequence, conserved in all eukaryotes, associated with increased ribonucleotide incorporation. Because these ribonucleotides can cause genome instability, this conservation is justified only if ribonucleotide incorporation serves a positive function as well. The researchers hypothesized that strand signaling for MMR could be one such positive function.

Using the yeast *Saccharomyces cerevisiae*, the researchers demonstrated that ribonucleotide excision repair was necessary for optimal MMR, and that variants of the leading strand DNA polymerase, which incorporate more

or less ribonucleotides than the wild type, have correspondingly more or less efficient MMR. Together, the data suggest that ribonucleotides contribute to marking the newly copied DNA strand for MMR. **(HF)**

Citation: Lujan SA, Williams JS, Clausen AR, Clark AB, Kunkel TA. 2013. Ribonucleotides are signals for mismatch repair of leading-strand replication errors. Mol Cell 50(3):437-443.

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Beta-arrestin-2 is major player in development of abdominal aortic aneurysm

NIEHS researchers determined that the signaling protein beta-arrestin-2 contributes to formation of abdominal aortic aneurysm (AAA) in mice. In humans, AAA is a largely asymptomatic, but potentially life-threatening disease that affects the aorta, the largest artery in the body. Currently, there are no pharmacological treatments available for AAA, but the present study offers a possible therapeutic breakthrough, by suggesting that beta-arrestin-2 may be a target for designing new drugs.

The authors used a mouse model of AAA, which involves the infusion of angiotensin II hormone in mice deficient for beta-arrestin-2. They observed a reduction in the incidence and severity of aneurysm formation. The underlying mechanism for beta-arrestin-2-mediated AAA formation was the activation of extracellular signal-regulated kinases that regulate expression of proinflammatory enzyme, cyclooxygenase-2 (COX-2). The beta-arrestin-2 deficiency diminished expression of COX-2 and other inflammatory factors, and it reduced macrophage infiltration in the aortas.

Angiotensin II leads to AAA development, by activating a G-protein coupled receptor AT1a, which can also form a complex with beta-arrestin-2. The new findings suggest that beta-arrestin-2 contributes to aneurysm formation through a G-protein-independent AT1a signaling pathway. Since both pathways are pharmacologically different, it offers a promise of potential new treatments. **(AA)**

Citation: Trivedi DB, Loftin CD, Clark J, Myers P, DeGraff LM, Cheng J, Zeldin DC, Langenbach R. 2013. Beta-arrestin-2 deficiency attenuates abdominal aortic aneurysm formation in mice. Circ Res 112(9):1219-1229.

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The role of p53 during bacterial pneumonia

NIEHS researchers recently discovered that the transcription factor p53 modulates host defense through regulating microbicidal function and fate of phagocytes during bacterial pneumonia. This study revealed a fundamental link between defense of genome and of host during environmental insult.

The authors used mice that had their p53 genes deleted (p53-/-) or in which p53 was pharmacologically inhibited. Both sets of mice displayed enhanced clearance of extracellular bacteria during pneumonia. The lungs of p53-/- mice displayed genome-wide induction of NF-kappaB response element-enriched proinflammatory genes in the steady state, and enhanced induction of cytokines upon infection. In addition, upon infection, p53-deficient mice exhibited increased influx of neutrophils into the airway, as well as enhanced nitric oxide

generation in the airway. p53-deficient neutrophils displayed enhanced microbicidal function. Despite enhanced bacterial clearance, infected p53-/- mice suffered increased mortality from pneumonia, likely due to aggravated lung injury from an overexuberant immune response.

Since p53-activating agents are widely used in human cancer therapy, the authors urge researchers to define the effects of pharmacologic activation of p53 on the human innate immune response *in vivo*. They also suggest that future studies should determine whether genetic polymorphisms leading to hypofunction of the p53 pathway are associated with increased risk for lung injury or mortality during human pneumonia. **(MM)**

Citation: Madenspacher JH, Azzam KM, Gowdy KM, Malcolm KC, Nick JA, Dixon D, Aloor JJ, Draper DW, Guardiola JJ, Shatz M, Menendez D, Lowe J, Lu J, Bushel P, Li L, Merrick BA, Resnick MA, Fessler MB. 2013. p53 integrates host defense and cell fate during bacterial pneumonia. J Exp Med 210(5):891-904.

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Phenobarbital directly binds to EGFR to activate CAR in the liver

In a collaborative effort involving the Pharmacogenetics Section and the Computational Chemistry-Molecular Modeling Support Group, NIEHS scientists identified the mechanism by which the barbiturate phenobarbital activates the constitutive active androstane receptor (CAR). They demonstrated that phenobarbital directly binds to the epidermal growth factor receptor (EGFR) to block a signaling cascade that prevents CAR activation. Because of the potential widespread applicability of this mechanism of drug activation, these results could have broad implications for human health.

The researchers demonstrated that activation of the EGFR pathway prevented the dephosphorylation and activation of CAR in primary mouse hepatocytes. Using extensive biochemical techniques, they showed that the scaffold protein RACK1 plays a key role, acting as a mediator between EGFR and CAR. Further, through isothermal titration calorimetry, binding analyses, and molecular modeling, they revealed that phenobarbital directly binds to EGFR in a manner that inhibits its activation. Thus, phenobarbital activates CAR by blocking the inhibitory actions of EGFR on CAR.

This study has resolved an issue that has plagued the field of phenobarbital research for more than 50 years, by identifying EGFR as its receptor. It also provides novel insight as to how phenobarbital activates CAR to mediate its physiological actions. **(HF)**

Citation: Mutoh S, Sobhany M, Moore R, Perera L, Pedersen L, Sueyoshi T, Negishi M. 2013. Phenobarbital indirectly activates the constitutive active androstane receptor (CAR) by inhibition of epidermal growth factor receptor signaling. Sci Signal 6(274):ra31.

(Aleksandra Adomas, Ph.D., is a research fellow in the NIEHS Laboratory of Molecular Carcinogenesis. Heather Franco, Ph.D., is an Intramural Research Training Award fellow in the NIEHS Laboratory of Reproductive and Developmental Toxicology. Mallikarjuna Metukuri, Ph.D., is a research fellow in the NIEHS Laboratory of Signal Transduction.)

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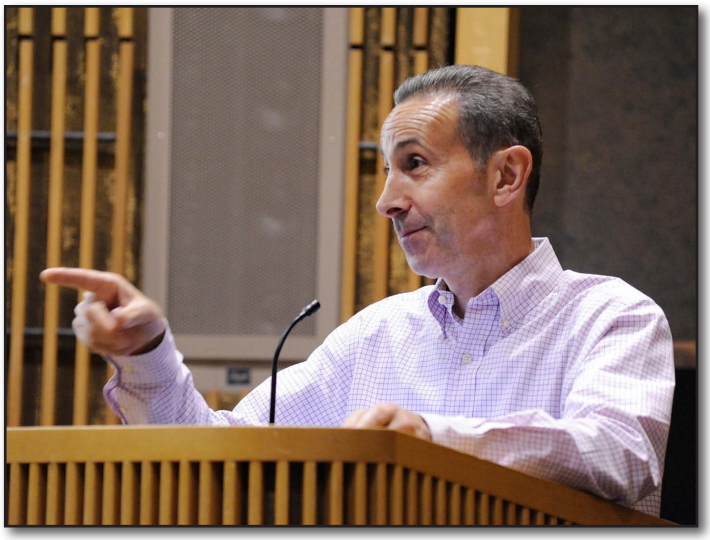
Inside the Institute

Zeldin urges proactive learning among 2013 summer interns

By Ian Thomas

"Experience is why you're here, so don't be afraid to pick up the phone and get involved."

That was the opening day message June 13 from NIEHS Scientific Director Daryl Zeldin, M.D., to this year's crop of students in the NIH Summer Internship Program (SIP) at NIEHS. Operating from June through August, the SIP gives high school and college students interested in biomedical science the chance for hands-on learning in a world-class research setting, by pairing them with mentors from the NIEHS intramural science team.



Zeldin opened his talk with a collection of comedic images from his childhood and college years. (Photo courtesy of Steve McCaw)

"During the next several weeks, you're going to experience a lot, so don't be shy about asking questions," Zeldin added. "Ultimately, your time here will be what you make of it, so be proactive and get involved in everything that you can."

Education by experiences

Throughout the summer, students will rum the gamut of activities, from seminars and career panels to extensive lab-time with an active role in real research — all designed to help students sample the different career paths the field has to offer.

Schelp works as a special assistant for NIEHS community outreach programs and deals extensively with students and educators from around the Triangle. (Photo courtesy Steve McCaw)

"Environmental health is an extremely broad subject," said Zeldin, who named DNA repair, bioinformatics, and clinical research as just a few examples. "Some of these you'll find interesting, and some you won't. The trick to success in this field is finding that one specific area that most excites you, then building your career on it."

As in years past, the highlight of the program comes in late July when students get to showcase their newfound research skills via the summer-ending poster session before mentors and peers in Rodbell Auditorium.

The history of the NIEHS mission

In addition to Zeldin's breakdown of NIEHS infrastructure, including its intramural and extramural research divisions plus the National Toxicology Program, students also received an in-depth explanation of the institute's mission.

"Some organizations, such as pharmaceutical companies, spend money on drugs to treat things like asthma," said John Schelp, a member of the NIEHS Office of Science Education and Diversity. "Our mission here is to understand what in the environment triggers asthma so we can try to prevent it altogether."

A noted area-historian and longtime resident of Durham, Schelp also spoke of history of NIEHS within the local community.

"In the mid-1960s, 48 states competed to get NIEHS before it eventually settled into an old tobacco field right here in North Carolina," he explained. "Six weeks later, IBM became the next major tenant to join NIEHS in the new Research Triangle Park, and RTP has been here ever since."

Looking ahead

"Between now and the fall, you'll be exposed to everything from bench-work in a lab to clinical research," said Zeldin, who elaborated on some of the pros and cons of earning an M.D. versus a Ph.D. "The hope is that by the time you leave here, you'll have found that niche that's right for you, and you'll then be able to use that to guide your studies moving forward."

From left to right, interns Meredith Parker, Thomas Woo, and John Parker listened as Schelp chronicled NIEHS history as a research institute. (Photo courtesy Steve McCaw)

Education takes center stage at internship career panel

This year's internship class reassembled on Thursday June 20 in Rodbell Auditorium for the SIP's annual career exploration panel — a two-hour Q&A session allowing students to interact with experts from across the biomedical research field.

This year's panelists included:

- Mercedes Arana, Ph.D. (NIEHS)
- Michael Fessler, M.D. (NIEHS)
- Mike Humble, Ph.D. (NIEHS)
- William Higgins, Ph.D. (University of Maryland)

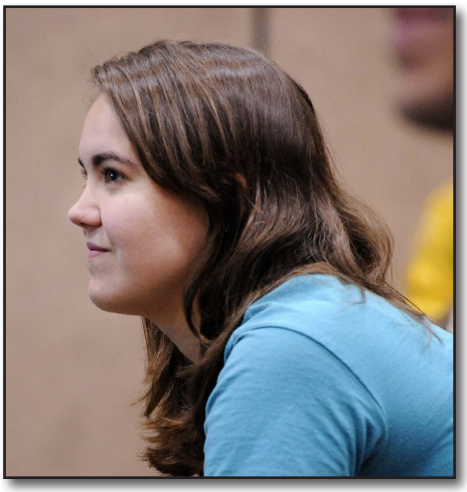
Among the major subjects of discussion was the pending decision of many students on graduate school versus medical school after graduation.

"I began as a pre-med major in undergrad, but took a job in a lab to help pay for my studies and loved it from the start," said Arana, a biologist with NIEHS who encouraged students to get involved in everything they could while in school. "Even once you decide on a career path, having a diverse background of experiences still helps you in a lot of ways, particularly if you ever hope to run your own lab."

Still, while research topics and fields of study were obviously hot topics of interest, the panelists agreed that students should never forget the basics.

"No matter what you choose to do for a living, take the time to learn to read, write, and speak effectively," said Higgins, an associate professor with the University of Maryland's biology department. "So many of our students today don't spend enough time developing these simplest of skills, and they're absolutely vital to success in any field, public health included."

Like their SIP colleagues, Scholars Connect interns Melissa Kerr, left, and Toyosi Oyelowo clearly enjoyed their orientation. (Photo courtesy Steve McCaw)



Elena Douglass listened as Zeldin explained the many learning opportunities the interns will encounter throughout the summer. (Photo courtesy Steve McCaw)

Intern Willa Chen reflected on the possible career paths ahead. (Photo courtesy of Steve McCaw)

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

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Records set on family day at NIEHS

By Eddy Ball

More than 100 youngsters, ranging from toddlers to teens, enjoyed fun, exercise, and creative learning June 20 at the 2013 NIEHS Bring Your Family to Work Day. Organized by the NIEHS Administrative Services and Analysis Branch Employee Services (ES) Group and Health and Safety Branch (HSB), the event mobilized scientists, administrators, and other employees from across the Institute as volunteers, to make the event a resounding success that set new records for the annual program.

Nature did its part as well, with one of the most pleasant summer days imaginable, encouraging NIEHS parents and their children to play on the lakeside patio — throwing Frisbees, frolicking at the Be Active Kids Playmobile, strolling along the lake as part of a scavenger hunt and nature walk, and competing in the annual cakewalk.

Just before lunch, younger visitors moved inside for the first in a series of fun science-learning activities with the Science of Sound, as teens explored Career Options in the Biomedical Sciences. Following a lunch break that featured a welcome from NIEHS and NTP Director Linda Birnbaum, Ph.D., the learning fun continued.

Along with tours of NIEHS, the afternoon highlighted science with a hands-on and humorous twist, with sessions on Who Ate the Cake, Fun With Histology, Waters the Matter Here, Allergies and the Family, MRI and Magnets, and U N ME N UV (You and Me and Ultraviolet).

For most of the temperate June morning, kids, little and not so little, played on the grass beside the lake. Some visitors entertained themselves with making bubbles. (Photo courtesy of Steve McCaw)

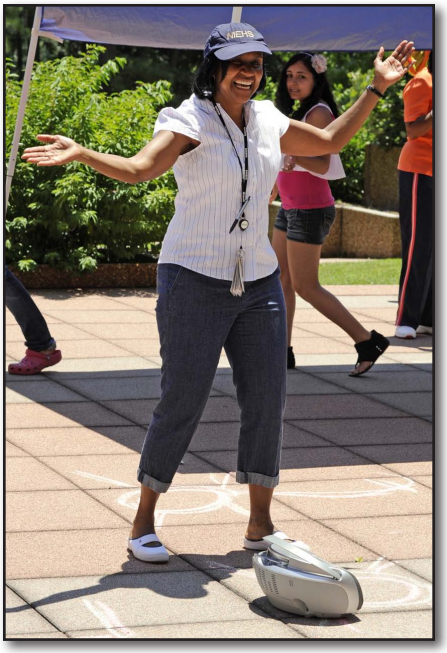
Others enjoyed activities closer to the ground. (Photo courtesy of Steve McCaw)

For ES staffers Jenn Evans, left, and Cynthia Radford, the hard work paid off handsomely, with an opportunity to get in touch with their inner child. (Photo courtesy of Steve McCaw)

The playful mood was infectious, as normally serious-minded scientists hit the turf to show off their athletic skills. Research fellow Jessica Williams, Ph.D., above, tried her hand at pitching a disk. (Photo courtesy of Steve McCaw)

Lead researcher Mike Fessler, M.D., enjoyed the opportunity for some quality time with his children, during normally busy working hours. (Photo courtesy of Steve McCaw)

Like many family and employee events at NIEHS, this one featured a welcome from Birnbaum, who reminisced about bringing her daughter Lisa to work, as part of the same program 25 years earlier. (Photo courtesy of Steve McCaw)



HSB industrial hygienist Vee Vee Shropshire was on the job to make sure everyone played safely — and to enjoy some quality time herself outdoors with the kids. (Photo courtesy of Steve McCaw)

The cakewalk is always a big draw, and this year was no exception. (Photo courtesy of Steve McCaw)

Meanwhile, the fun continued indoors, as ES staffer Dick Sloane, right, and a team of volunteers introduced concepts of sound in their Science of Music presentations. (Photo courtesy of Steve McCaw)

As soon as the little ones learned they could even see sound on the oscilloscope, a line formed of kids waiting their turn to play. (Photo courtesy of Steve McCaw)

As Bring Your Child to Work Day came to a close, ES manager Ed Kang and son Ian showed just how much fun everyone had playing and learning. (Photo courtesy of Steve McCaw)

Program administrator Mike Humble, Ph.D., was one of many NIEHS volunteers who left their computers and experiments behind, as they jumped in to help the kids with science activities. (Photo courtesy of Steve McCaw)

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National Institute of Environmental Health Sciences

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