National Institute of Environmental Health Sciences

Environmental Factor

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September 2013

NIEHS Spotlight

Partners advance justice and parity in environmental public health

More than 230 participants gathered for the Environmental Health Disparities and Environmental Justice Meeting July 29-31 at NIEHS in Research Triangle Park, N.C.

Stakeholders weigh in on environmental public health

The Environmental Health Disparities and Environmental Justice Meeting July 29-31 was designed to foster multidirectional communication among participants.

Birnbaum keynotes at National Environmental Monitoring Conference

NIEHS and NTP Director Linda Birnbaum, Ph.D., found herself on familiar turf Aug. 6 as she presented one of three keynote addresses at a meeting in San Antonio.

NIEHS fellow begins career in life science consulting

In August, NIEHS postdoctoral fellow Georgette Charles, Ph.D., moved from the bench to a position with AVOS Consulting, a division of INC Research in Raleigh.

Science Notebook

Birnbaum lab premieres publication on flame retardant additive Audio

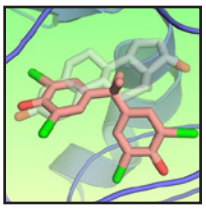
The study, published in the August issue of Toxicological Sciences, focuses on beta-HBCD and the effects of the flame retardant chemical on female mice.

Metabolomics symposium highlights the field's triumphs and challenges

RTI hosted the NIH Eastern Regional Comprehensive Metabolomics Resource Core Symposium Aug. 9 at its Research Triangle Park, N.C. headquarters.

Trainees' research recognized at SSR annual meeting

Work by three trainees in the NIEHS Reproductive Developmental Biology Group won top honors at the Society for the Study of Reproduction meeting July 19-23 in Montreal.



3-D images show flame retardants can mimic estrogens

NIEHS researchers have discovered how some commonly used flame retardants, called brominated flame retardants, might possibly disrupt the endocrine system.

Study finds wide range in pregnancy length

Researchers in the NIEHS Epidemiology Branch found a much broader range in the length of human pregnancies than is usually considered average.

NIEHS Spotlight

Veteran grantee named to Washington State Academy of Sciences

NIEHS grantee Michael Smerdon, Ph.D., is one of 24 scientists elected this year as members of the Washington State Academy of Sciences.

NIEHS researcher Donald Cook receives tenure

Donald Cook, Ph.D., has been with the NIEHS Laboratory of Respiratory Biology since 2005, studying how inhaled allergens and environmental pollutants affect the lungs.

NIEHS awards Superfund occupational and safety training grants

The NIEHS-funded Superfund Research Program welcomes newly funded Occupational and Safety Training Education Programs on Emerging Technologies.

NIEHS welcomes Nanjing Medical University delegation

Chinese public health scientists are pursuing a Memorandum of Understanding with leading U.S. biomedical research centers at Harvard, Johns Hopkins, and NIEHS.

Balbus facilitates IOM webinar series

NIEHS Senior Advisor for Public Health John Balbus, M.D., played a leading role in a three-part webinar this summer on global health and sustainable development.

Science Notebook

DNA glycosylases in action — the search for damaged bases

In an Aug. 5 talk at NIEHS, cancer researcher Susan Wallace, Ph.D., described her latest findings on a process that influences cancer susceptibility and carcinogenesis.

Webinar highlights advances in the study of autism Video

Two NIEHS-funded scientists — Judy Van de Water, Ph.D., and Rebecca J. Schmidt, Ph.D. — are making significant strides in unraveling the mystery of autism.

NTP talk explores zebrafish as a vertebrate model in toxicity screening Video

Arantza Muriana, Ph.D., gave a presentation Aug. 19 on the utility of zebrafish for toxicity testing, hosted by the Toxicology and Biomolecular Screening Branches.

N.C. industrial livestock workers found to carry drug-resistant bacteria

Industrial livestock operations that use subtherapeutic doses of antibiotics could expose workers to drug-resistant bacteria, according to a new study co-funded by NIEHS.

Zebrafish developmental assays test the safety of new chemicals

A group of molecules developed to break down pollutants in water is one step closer to commercial use, thanks to developmental testing led by a Superfund researcher.

NIEHS Spotlight

Duke SRP uses blog to explain research projects

This summer, the Duke University Superfund Research Program has ramped up postings on its blog, ToxInsider, to explain NIEHS-funded research findings.

Iowa SRP hosts health science and engineering summer camp

High school students from across the country explored environmental health topics and learned more about scientific research at a weeklong summer camp.

Science Notebook

Inhibitors of DNA topoisomerase and its repair enzymes in cancer treatment

Fellows of the Laboratory of Molecular Genetics welcomed pharmacologist Yves Pommier, M.D., Ph.D., for a talk on cancer therapeutic research Aug. 12 at NIEHS.

This month in EHP

This month, Environmental Health Perspectives focuses on advances in combating aflatoxins in the food supply and explores the gut microbiome in health and disease.

Inside the Institute

Feds Feed Families sets new record with 2013 food drive

NIEHS employees concluded the 2013 Feds Feed Families campaign with its final collection Aug. 28, for a total of 3,612 pounds of donated food and hygiene items.

Friends and colleagues remember Walter Olds

Friends and colleagues were saddened by news of the death Aug. 22 of NIH retiree Walter Olds at age 87 in Cary, N.C.

Extramural Research

Extramural papers of the month

- Cigarette smoke affects genes associated with heart and lung health
- Graphene sheets pierce and enter cells
- Global cost of childhood lead exposure
- Understanding the cytotoxicity of hexavalent chromium

Intramural Research

Intramural papers of the month

- APOBEC cytidine deaminases generate many mutations in human cancers
- Observing a DNA polymerase using time-resolved crystallography
- How specific stressors alter p53 binding and transactivation
- Early mouse development influences norepinephrine neuron diversity

Calendar of Upcoming Events

- **Sept. 3**, in the Executive Conference Room, 12:00-1:00 p.m. — Receptor Mechanisms Discussion Group Seminar Series presentation on “New Roles for an Old Receptor: AHR Function in Hepatic Progenitor Cells and Non-genomic Regulations of Metabolic Pathways,” by Russell Thomas, Ph.D.

- **Sept. 6**, in Rodbell A, 11:00 a.m.-12:00 p.m. — Laboratory of Reproductive and Developmental Toxicology Seminar Series, featuring Folami Ideraabdullah. Ph.D., speaking on “Identifying Heritable Mechanisms of Epigenetic Response to Environment”

- **Sept. 6 (offsite event)**, in the Levine Science Research Center, Room 247, Duke University, 12:00-1:00 p.m. — Integrated Toxicology and Environmental Health Program Fall 2013 Seminar Series, featuring Bruce Blumberg, Ph.D., speaking on “Obesogens, Stem Cells, and the Transgenerational Programming of Obesity”

- **Sept. 10**, in Rodbell Auditorium, 8:30 a.m.-3:30 p.m. — National Advisory Environmental Health Sciences Council meeting

- **Sept. 11**, webinar, 1:00-2:30 p.m. — U.S. Environmental Protection Agency-NIEHS Children’s Centers 2013 Webinar Series, focus on asthma, featuring Andrew Liu, M.D., and Rob McConnell, Ph.D. http://www.epa.gov/ncer/childrenscenters/webinar/2013/overview.html

- **Sept. 13 (offsite event)**, in the Levine Science Research Center, Room 247, Duke University, 12:00-1:00 p.m. — Integrated Toxicology and Environmental Health Program Fall 2013 Seminar Series, featuring Elena Braithwaite, Ph.D., speaking on “Metal-Regulatory Transcription Factor 1 — Its Interacting Partners and Downstream Targets”

- **Sept. 20 (offsite event)**, in the Levine Science Research Center, Room 247, Duke University, 12:00-1:00 p.m. — Integrated Toxicology and Environmental Health Program Fall 2013 Seminar Series presentation on “Toxins and Genes: A New Perspective in Gene-Environment Interactions in Schizophrenia,” by Tomas Guilarte, Ph.D.

- **Sept. 20**, in Rodbell Auditorium, 2:00-5:00 p.m. — National Postdoctoral Appreciation Day

- **Sept. 23**, in Rodbell Auditorium, 11:00 a.m.-12:00 p.m. — Laboratory of Molecular Genetics Fellows’ Invited Guest Lecture featuring Craig Cameron, Ph.D., topic TBA

- **Sept. 24**, in Rodbell Auditorium, 8:30 a.m.-5:00 p.m. — SACATM meeting

- **Oct. 1**, in the Executive Conference Room, 12:00-1:00 p.m. — Receptor Mechanisms Discussion Group Seminar Series presentation on “Progesterone Action on Normal and Abnormal Human Endometrium,” by Steven Young, M.D., Ph.D.

- View More Events: NIEHS Public Calendar

NIEHS Spotlight

Partners advance justice and parity in environmental public health

By Ernie Hood

Building on the rich NIEHS legacy of research and initiatives addressing the environmental component of health disparities, more than 230 participants gathered July 29-31 for the Environmental Health Disparities and Environmental Justice Meeting at NIEHS in Research Triangle Park, N.C.

The event brought together grantees, community partners, health care professionals, and government representatives from federal and state agencies, along with potential new partners in research. The meeting was an ideal setting to share, listen, and promote best practices of current and past environmental health disparities and environmental justice research, while also focusing on emerging issues and new directions in the field (see meeting booklet for the agenda, abstracts, and additional resources).

Representatives from several federal agencies organized the meeting, including NIEHS, spearheaded by NIEHS Partnerships for Environmental Public Health leads Program Analyst Liam O'Fallon and Health Scientist Administrator Symma Finn, Ph.D., who worked collaboratively with the U.S. Environmental Protection Agency (EPA); the National Institute on Minority Health and Health Disparities (NIMHD); the Centers for Disease Control and Prevention; and the U.S. Department of Health and Human Services Office of Minority Health and Indian Health Service.

"We envisioned the meeting as an opportunity to facilitate and strengthen ties among federal partners, and to create connections among the grantees supported by those different agencies," said O'Fallon.

Building on a foundation of synergy

With such a diverse group of participants and a wide-ranging agenda, the meeting achieved a critical mass of enthusiasm and commitment to advancing work on health disparities, as NIEHS and NTP Director Linda Birnbaum, Ph.D., observed in her opening remarks.

Twin themes shape historic meeting

A deep-seated commitment to civil rights informs the pillars of justice and parity in environmental public health community-based participatory research.

Environmental Health Disparities (EHD)

EHD programs address the unique contribution of the environment to health disparities, which are preventable differences in the burden of disease, injury, violence, or opportunities to achieve optimal health that are experienced by socially disadvantaged populations.

Environmental Justice (EJ)

EJ initiatives promote the fair treatment and meaningful involvement of all people with respect to the development, implementation, and enforcement of environmental laws, regulations, and policies.

Birnbaum shared her impression of the meeting. "[This will be] an opportunity for us to build upon our collective work, strengthen our partnerships, identify the historical issues that require our attention, note emerging issues, and prioritize next steps, and to move forward not only as big groups but as individuals, to ensure that environmental injustice and disparities eventually become things of the past." (Photo courtesy of Steve McCaw)

"By working together, we can make the whole much more than the sum of the parts, by conducting research looking not only at the totality of exposures that people endure, but also factoring in new exposures and looking at issues of communication and capacity-building," she said. "With the commitment to community engagement, dialogue, and capacity-building of all partners, we can have lasting impacts and improved public health."

Noting that there is a growing body of evidence pointing to the significant influence of non-biological factors, such as social and environmental determinants, NIMHD Director John Ruffin, Ph.D., expressed similar sentiments in his welcoming remarks. "Bringing together such a diverse group of partners and interested collaborators suggests that you recognize the importance of integrating distinct and sometimes fragmented disciplines," he said. "That has been our mantra at NIMHD, because we realize that it will take more than NIMHD and more than NIH to address health disparities."

O'Fallon, left, and Ruffin listened to Birnbaum's presentation. Ruffin, who spoke next, described the long-standing partnership between NIMHD and NIEHS, as the institutes have worked together for many years to pioneer research on environmental health disparities and programs on environmental justice. (Photo courtesy of Steve McCaw)

Dovetailing with the strategic plan

As Finn explained, the meeting was designed to promote the implementation of the NIEHS strategic plan goals, particularly goal 6, which focuses on establishing a research agenda related to environmental health disparities, and goal 11, which promotes communication and collaboration among researchers and stakeholders in environmental health sciences. But, with its emphasis on collaborations, partnerships, and integration, there was more to the meeting than simply presentations on the issues, she explained.

"We framed a lot of the sessions in terms of NIEHS strategic goals, but it was a little more open-ended," Finn told the participants. "Sometimes we tend to put things into categories and then try to fit people's needs and concerns into those categories, but this was more about asking what's out there in the community and how we can actually use research to address health disparities."

The meeting's format enhanced the empowerment of the community members and partners (see related story), with three sets of concurrent sessions and an extensive report-back session in which participants in the twelve breakout groups developed concrete recommendations — to-do lists that will help set the tone and course for measurable progress.

National Center for Environmental Research Director James Johnson Jr., Ph.D., welcomed meeting attendees on behalf of the EPA, one of the conference's organizing bodies. (Photo courtesy of Steve McCaw)

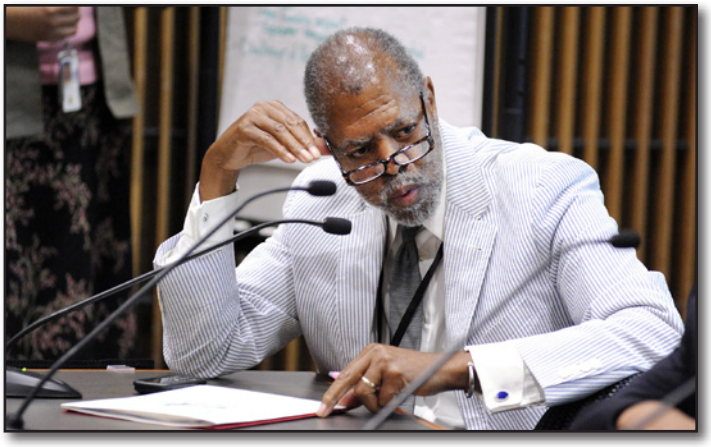
(Ernie Hood is a contract writer with the NIEHS Office of Communications and Public Liaison.)

Keynote speaker Marie Lynn Miranda, Ph.D., dean of the School of Natural Resources and Environment at the University of Michigan, formerly of Duke University, set the tone for the meeting with her keynote address, "It Takes a Village: Integrated Methods for Addressing Environmental Health Disparities." (Photo courtesy of Steve McCaw)

Silent Spring Institute Executive Director Julia Brody, Ph.D., awaited the opportunity to join the discussion during one of the meeting's general sessions. Brody is an NIEHS grantee and member of the National Advisory Environmental Health Sciences Council. (Photo courtesy of Steve McCaw)

Finn, left, took advantage of a break to talk with grantee Chensheng (Alex) Lu, Ph.D., of Harvard University, about his project on children's exposure to pesticides in produce. (Photo courtesy of Steve McCaw)

Joan Packenham, Ph.D., director of the NIEHS Office of Human Research Compliance, co-moderated the session on Institutional Review Boards and Community Engaged Research: How Can Universities and Community Organizations Work Together to Strengthen the Ethics Review of Community Based Research? (Photo courtesy of Steve McCaw)



Former NIEHS and NTP Director Kenneth Olden, Ph.D., who is now director of the EPA National Center for Environmental Assessment, returned to the NIEHS campus to moderate one of the concurrent sessions devoted to using geographic and spatial analysis to help examine environmental determinants of health. (Photo courtesy of Steve McCaw)

University of Arizona (UA) graduate student Melissa Valdez described NIEHS-funded research on environmental literacy that she and Marti Lindsey, Ph.D., director of the UA Community Outreach and Education Program, conducted in collaboration with researchers from the University of Rochester. (Photo courtesy of Steve McCaw)

The breaks gave participants a chance to continue their dialogue, including NIEHS representatives Chip Hughes, left, director of the Worker Education and Training Program, and John Balbus, M.D., senior advisor for public health. (Photo courtesy of Steve McCaw)

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Stakeholders weigh in on environmental public health

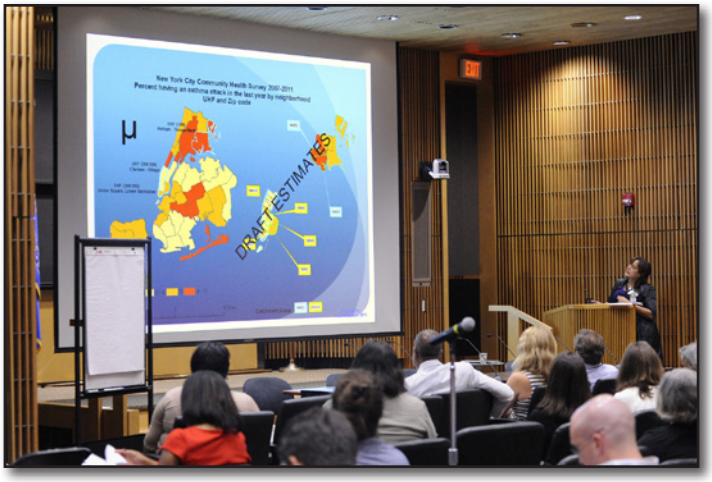
By Ernie Hood

From its inception, the Environmental Health Disparities and Environmental Justice Meeting July 29-31 was designed to foster multidirectional communication among participants. The community partners, academics, healthcare professionals, and federal agency representatives who attended had ample opportunities to interact with each other to an extent rarely seen in such gatherings, giving everyone an opportunity to provide input.

“People came to engage, to listen, and to share,” said co-organizer Liam O’Fallon, NIEHS Partnerships for Environmental Public Health program lead. ”We planned for an interactive meeting, so it was very gratifying to see the level of interaction and engagement of the meeting participants from all across the country.”

Scheduled for success

The meeting's format allowed myriad opportunities for attendees to work together effectively. Along with several general sessions, there was a series of concurrent sessions focused on solutions in specific areas, such as tools and technologies, capacity-building, persistent inequities in Native American communities, and culturally appropriate communication strategies. Those twelve sessions culminated in a report-back session at the end of the meeting's second day, when a representative of each group described each session's conclusions and recommended next steps.



Community-level mapping of GIS data contributes to the body of evidence linking social and physical environmental factors to adverse health outcomes. Beverly Xaviera Watkins, Ph.D., of Weill Cornell Medical College, described the research methods used by her community-academic research partnership to educate, advocate, and organize in New York's impoverished Lower East Side. (Photo courtesy of Steve McCaw)

"The meeting was a lot more than just listening to presentations," said co-organizer Symma Finn, Ph.D., NIEHS health scientist administrator. "People were discussing what were the key issues that we need to remain focused on, so the slides from the report-back session are not so much a recommendation list, as a to-do list."

The report-back session was followed by a poster session, where 35 different academic and community groups had the opportunity to share their achievements and findings.

Former NIEHS and NTP Director Kenneth Olden, Ph.D., left, moderated a panel discussion on the use of geographic and spatial analysis, to examine environmental determinants of health and engage communities around environmental public health issues. He was joined, from left, by panel members Sacoby Wilson, Ph.D., from the University of Maryland; Paul Juarez, Ph.D., of the University of Tennessee Health Science Center; and Watkins. (Photo courtesy of Steve McCaw)

Day three of the meeting was devoted entirely to workshops, where community members demonstrated how to effectively engage communities, based on their own experiences in the field. Finn was particularly excited about the workshops, as community partners shared best practices, successes, and challenges.

The workshops covered a wide range of approaches used in community engagement, including a workshop, Do No Harm, based on the experiences of the North Carolina Environmental Justice Network, and a session, Theatre of the Oppressed, that was highly effective at breaking down barriers to communication. Other workshops featured grassroots reports from community groups in health disparate communities in Southern California, Louisiana coastal communities, New York's Lower East Side, and the inner city of Philadelphia.

Power to the partners

Throughout the meeting, the emphasis was on the power of partnerships to effect change. NIEHS scientist Christine Ekenga, Ph.D., who moderated the concurrent session Cumulative Exposures: The Role of

Epidemiology in Elucidating Environmental Contributions to Health Disparities, powerfully expressed the sentiment during the report-back session.

"The take-away message from our session and from this entire conference is don't underestimate the power of community members and researchers working together," Ekenga said. "When you have community members and the public supporting the work, it's a powerful combination, and it's important for us not to underestimate that power."

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

Closing out the general session July 30 on Challenges and Opportunities for Supporting Community-Based Research to Address Environmental Health Disparities and Environmental Justice, attendees were asked to participate in a unique neighbor-to-neighbor discussion period, to make new connections and come up with new ideas. (Photo courtesy of Steve McCaw)

During the animated neighbor-to-neighbor discussion, Laurel Schaider, Ph.D., right, of the Harvard School of Public Health, shared insights from her work on metal mixtures and children's health with Donele Wilkins, of the Green Door Initiative in Detroit. (Photo courtesy of Steve McCaw)

The meeting drew a capacity audience of community partners from as far away as Alaska and Hawaii, including Viola Waghiyi, director of the Environmental Health and Justice Program for the Alaska Community Action on Toxics and a member of the National Advisory Environmental Health Sciences Council. (Photo courtesy of Steve McCaw)

Ekenga, a postdoctoral fellow in the Epidemiology Branch at NIEHS, reported the results of the concurrent session on cumulative exposures. (Photo courtesy of Steve McCaw)

The meeting included lively Q&A periods during the concurrent and workshop sessions. Above, Wig Zamore of the Somerville Transportation Equity Partnership in Massachusetts, responded to a point made during a panel discussion. (Photo courtesy of Steve McCaw)

"The poster session allowed for that higher level of interaction and discussion that meetings are supposed to achieve and often do not," Finn observed. "This meeting was set up to promote people just being able to talk to each other, and it worked. The poster session was a perfect example." (Photo courtesy of Steve McCaw)

John Doyle of the Crow Environmental Health Steering Committee (CEHSC), Little Big Horn College in Montana, discussed his group's poster, "Addressing Disparities in Safe Drinking Water Access on the Crow Reservation, Montana," with Finn. The poster described lessons learned in conducting community-based participatory research on water quality in the Crow tribal community through the CEHSC, and in working to upgrade water and wastewater infrastructure in the complex legal and jurisdictional reservation environment. (Photo courtesy of Steve McCaw)

Linda Easley, Ph.D., left, of Siena Heights University, talked with Elizabeth Guzy, of the Harvard Superfund Program, about how inspiring this meeting was to her work among Latinos. (Photo courtesy of Steve McCaw)

Neasha Graves, left, of the University of North Carolina at Chapel Hill, discussed outreach and communication with Marti Lindsey, Ph.D., of the University of Arizona. (Photo courtesy of Steve McCaw)

Miller described her program in Alaska as part of the panel session on Challenges and Opportunities for Supporting Community-based Research to Address Environmental Health Disparities and Environmental Justice. Also pictured is panel presenter, Thomas Arcury, Ph.D., of Wake Forest University. It was one of several opportunities for participants to engage their colleagues in open-ended Q&A sessions. (Photo courtesy of Steve McCaw)

Nuts and bolts from the grassroots

One of the presentations during the meeting's general session devoted to discussion of challenges and opportunities associated with community-based research exemplifies the action-oriented and pragmatic nature of the proceedings. Pamela Miller, executive director of Alaska Community Action on Toxics, described her group's mission and activities.

"We are a small, non-profit environmental health and justice research and advocacy organization. We do community-based participatory research at the invitation of communities throughout Alaska. We have conducted a lot of focused work on St. Lawrence Island in the northern Bering Sea, but we also work with other communities who requested our assistance, and we try to transform these requests for assistance into some type of systemic change, whether that's interventions in the community or some policy-level changes. We hold workshops, we do community-based outreach, training, and education, and we provide technical assistance and capacity-building."

Miller also talked about how her group has not only survived, but also thrived.

"I think all community-based organizations have found that it's a really tenuous thing to try to sustain the work that we do in the community. I think the way that we've gotten through some hard times is by making a deliberate effort to diversify our funding base, to really cultivate community support for the work that we do. We've not only raised funding through members, major donors, and foundation partners, but in the last couple of years we've tried some new approaches to do mission-related enterprises that hopefully not only provide jobs for the environment, but also bring some resources back into our organization to support the work we do. We've started a green cleaning service that employs workers in the community, who are supported with sustainable jobs, to go out and do non-toxic cleaning in homes and businesses. We have an Anchorage Farmer's Market project where we sell compost tea and organic [vegetable] starts, and we have a community gardening program that also helps bring resources back into the organization."

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Birnbaum keynotes at National Environmental Monitoring Conference

By Eddy Ball

NIEHS and NTP Director Linda Birnbaum, Ph.D., found herself on familiar turf Aug. 6, as she presented one of three keynote addresses at a meeting in San Antonio.

Birnbaum spoke to attendees of the 2013 National Environmental Monitoring Conference (2013 NEMC) Aug 5-9 about "Linking Low Dose Exposure of Environmental Contaminants to Health Effects," kicking off the second of five days of talks, poster presentations, and training.

Reassessing conventional wisdom about dose response

In her presentation, Birnbaum explored the notion that less can be sufficient, or even more than enough, when it comes to the adverse health effects of exposure to environmental chemicals. As Birnbaum told the attendees, the conventional notion of dose response doesn't account for the effects of hormone-mimicking substances on the endocrine system or the implications of exposure to a range of other chemicals, even at low doses, during critical periods of development.

Birnbaum began with an examination of the endocrine system in humans and nonlinear dose response patterns for endocrine disrupting compounds (EDCs). Very small doses, measured in the parts-per-million and parts-per-billion range, she explained, can have profound effects on health and development.

"A one unit change in hormone concentration, in a low concentration range, may have a large — 50 percent — effect on receptor occupancy," she said, "while the same change in hormone concentration, in a higher concentration range, may have a small — 5 percent — effect on receptor occupancy. [As a consequence,] low-dose exposures to endocrine disruptors may be able to have profound impacts on receptor binding and activation, and, therefore, the downstream events that are controlled by those receptors."

According to Birnbaum, proponents of the low-dose hypothesis contend that a large number of recent studies now provide clear support for their hypothesis.

Translating measurements into risk assessment

2013 NEMC featured more than 133 oral and 29 poster presentations organized into concurrent technical sessions. Presentation topics ranged from optimizing U.S. Environmental Protection Agency (EPA) detection method instrumentation, to seasonal variation in the composition of air pollution.

Not surprisingly, EPA dominated the meeting, which is billed as the largest conference focused on environmental measurements in North America. Since 2006, NEMC has been co-sponsored by The NELAC Institute under a cooperative agreement with EPA.

The conference brings together scientists and managers from federal and state agencies, the regulated community, academia, and laboratory and engineering support communities. NEMC meeting agendas feature a balance of technical and policy topics related to data gathering, measurement, and risk assessment.

Timing also shapes dose response

When exposure occurs can influence the effects of exposure, Birnbaum continued, so that low-dose exposures need to be integrated into risk analysis. "Timing of exposure is critical. Exposure during development is not comparable to adults."

Birnbaum offered examples of the effects of what would be considered a low-dose arsenic exposure for a pregnant woman, on the health of her child, as he or she develops and grows into adulthood. She also referred to a new NTP monograph on the effects of low levels of lead on the growth and neurological, digestive, and sensory health of exposed children. Both arsenic and lead continue to be present in the environment, from natural and manmade sources, at doses that can impact health when exposure occurs at critical periods during development.

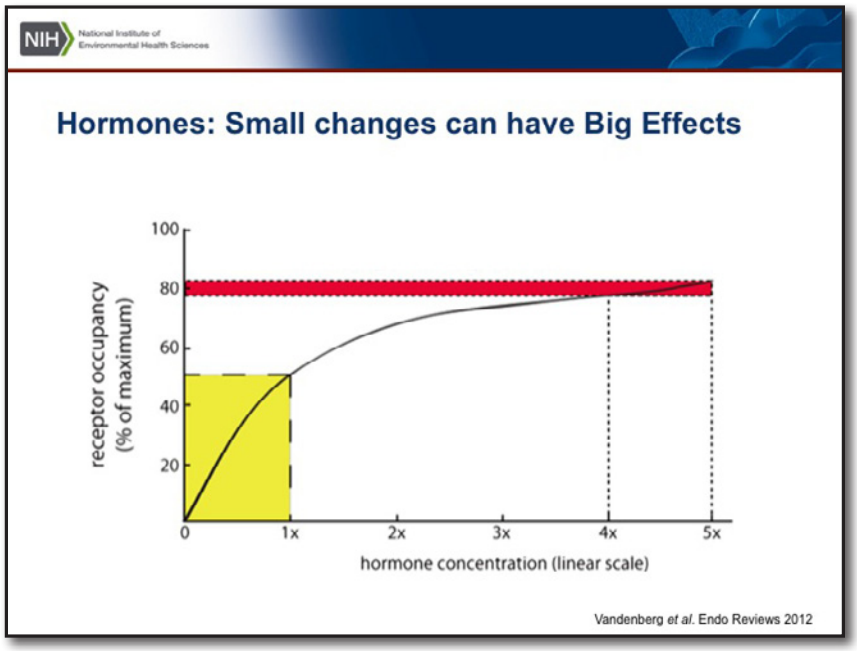
Returning to EDCs, Birnbaum outlined adverse effects on health, by exposure to a range of chemicals that are virtually everywhere in the environment. These include the plasticizing compounds phthalates and bisphenol A, fire retardant chemicals, and pesticides, such as chlorpyrifos and residues of DDT and related chemicals.

According to Birnbaum, newer studies, several funded by NIEHS, are leading to a reconsideration of the low dose hypothesis in light of their findings. (Photo courtesy of Steve McCaw)

Advancing toxicology study design

"Traditional high-dose toxicity studies may not be adequate to assess adverse effects from these hormonally active agents, in that they do not detect effects that are occurring at low doses," Birnbaum concluded.

Traditional toxicity studies have often not made developmental stage a consideration or adequately considered the significant differences between the response of individuals and populations. Birnbaum explained that future studies will need to integrate these typically overlooked considerations into more broadly applicable risk assessments of chemical exposures at physiological doses, comparable to those that might be expected from environmental exposure or to what is seen in diverse human populations.



In this slide from her presentation, Birnbaum shows how a low dose of a hormone or hormone-mimicking chemical has a disproportionately large effect on receptor occupancy (shown in yellow), while greater doses have a relatively smaller effect, as receptors become saturated. (Courtesy of Linda Birnbaum)

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NIEHS fellow begins career in life science consulting

By Aleksandra Adomas

Georgette Charles, Ph.D., completed her nearly three-year postdoctoral training in the NIEHS Laboratory of Molecular Carcinogenesis in August, to begin a new phase in her career at AVOS Consulting in Raleigh, N.C., a division of INC Research that specializes in strategic and financial market analysis for life sciences companies. Charles' new job will be diverse, potentially requiring her to design a market access strategy for a new drug, or provide analysis of existing business problems and develop plans for improvement.

Charles made attending networking events easier, at the beginning, by inviting a friend along, who most of the time was not a scientist, but was able to provide friendly support and make her more comfortable in unfamiliar situations. (Photo courtesy of Steve McCaw)

Bridging with the business world

"Acquiring business language is essential when planning a transition to the business world, long before a job interview invitation," Charles said of her job search. To become familiar with core corporate concepts, Charles attended biotech business seminars at the North Carolina Biotechnology Center, and entrepreneurship events at the University of North Carolina at Chapel Hill and Duke University. She was able to practice using professional terms and expand her understanding of financial issues, at educational and networking events in the area.

Interviewing with a consulting company is intense and requires business problem-solving abilities, in addition to a knowledge of the professional language. Charles honed her critical thinking skills with textbook case studies, as well as those published online by consulting companies. She was then able to compare her recommendations for tackling a problem with strategies developed by professionals.

Although most of the job applications Charles submitted during the final months of her job search came through her contacts and internal referrals, she found the AVOS job posting online. To prepare for her interview, Charles conducted extensive research on the company itself and on the acquisition by INC Research, which had been an AVOS client. This information allowed her to formulate a long list of questions that engaged the interviewers and demonstrated her interest in the position.

Self-assessment

Charles devoted the last two years of her postdoctoral experience to finding her niche in science, and identifying critical skills, values, and interests crucial for her future career path. One of the tools she found useful for this self-assessment was an individual development plan, such as the one available on the Science Careers website.

"I love science and hypothesis-driven research. I can delineate complex problems, pick them apart, and, at the end, present the results and deliverables," she explained. Charles also said she was looking forward to the team effort, developing long-term relationships with clients, and obtaining immediate feedback that are exemplified in the business consulting environment.

Having decided on life science consulting as a career, she focused on expanding her network. Charles quickly found out that her experience in stem cell research, because of its potential for clinical applications, generated interest and made informal conversations easier. Charles, together with mentor Guang Hu, Ph.D., NIEHS Stem Cell Biology Group lead researcher, identified a novel post-translational pathway that regulates self-renewal in mouse embryonic stem cells.

Charles credits reviewers at NIEHS career fairs and Tammy Collins, Ph.D., director of the NIEHS Office of Fellows' Career Development, with providing very constructive criticism about the content of her resume. She said that feedback from current business consultants, friends, and networking contacts was invaluable when developing her resume into the ideal business format. "It was a sometimes daunting process that took 3 to 4 months and reduced my 6-page resume to 1 1/2 pages that highlighted the necessary skills and experiences," she recalled.

(Aleksandra Adomas, Ph.D., is a research fellow in the NIEHS Laboratory of Molecular Carcinogenesis.)

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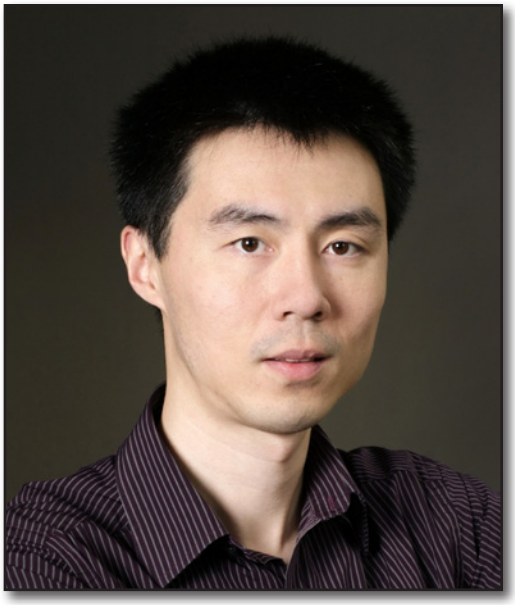


"Georgette's postdoctoral training helped her develop and improve her analytical skills, which are the top requirement for a consulting job," Hu said. "The career services and workshops NIEHS and LMC organized helped her get to know what career options there are and prepared her for future career." (Photo courtesy of Steve McCaw)

Veteran grantee named to Washington State Academy of Sciences

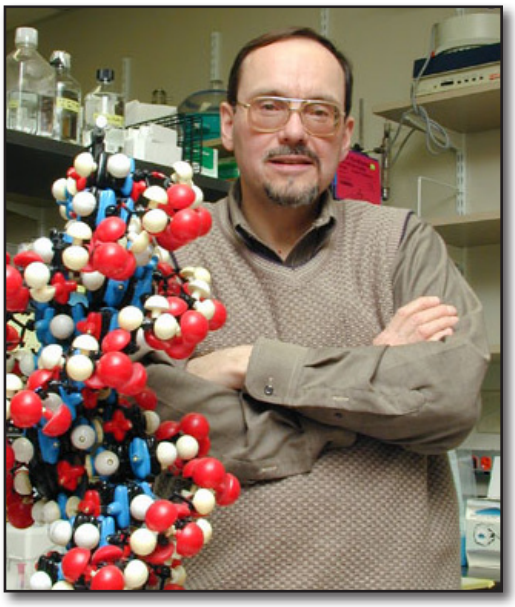
By Eddy Ball

NIEHS grantee Michael Smerdon, Ph.D., is one of 24 scientists elected this year as members of the Washington State Academy of Sciences. He joins two other colleagues from Washington State University (WSU), according to an Aug. 12 WSU press release.

Smerdon, a regents professor of biochemistry and biophysics, has had NIEHS support since 1978, when he received a Young Environmental Scientist Grant Award, following completion of his postdoctoral fellowship in pathology at Washington University School of Medicine in St. Louis.

The author of more than 100 peer-reviewed publications, Smerdon currently holds two NIEHS grants overseen by NIEHS Health Scientist Administrator Les Reinlib, Ph.D. — "Repair of carcinogen damaged DNA in human chromatin" and "DNA repair in a hormone responsive gene."

We are pleased to have sponsored Dr. Smerdon for many years," Reinlib said. "He is a shining example of an investigator producing insights that will lead to a comprehensive understanding of ways that environmental chemicals or harmful radiation attack DNA."



Smerdon is a pioneer in the area of DNA repair and chromatin packaging. When he was a postdoc and junior investigator, his papers were among fewer than 20 published each year on the subject. In 2012, there were nearly 450. (Photo courtesy of WSU)

Election to the Washington State Academy of Sciences is the most recent of many honors Smerdon has received for his teaching, research, and service. In 2012, he was honored by WSU with its Eminent Faculty Award. He was elected a fellow of the American Association for the Advancement of Science in 2010; received the Science and Engineering Alumni Leadership Award in 2003 from St. Cloud State University, his alma mater; and has been recognized several times for faculty excellence. In 2001, he was selected for prestigious NIH Method to Extend Research in Time (MERIT) Award, which provides up to 10 years of research funding to select leaders in their field.

The Washington State Academy of Sciences is the scientific organization established to offer advice on science policy in the state. At the invitation of the Washington State Legislature, it is preparing an independent white paper addressing the science underlying the use of products from genetically modified plants and animals in food, as well as the impacts of required labeling of foods containing ingredients from genetically modified organisms. The academy is also participating in the Puget Sound Partnership's efforts to protect and restore Puget Sound.

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NIEHS researcher Donald Cook receives tenure

By Robin Arnette

For many scientists, receiving tenure, or a permanent research position, is an important professional milestone. The appointment enables them to continue delving into the complexities of nature, while having some job security. One of the latest scientists at NIEHS to receive tenure is Donald Cook, Ph.D., a lead researcher in the Laboratory of Respiratory Biology. Cook has been at NIEHS since 2005 and studies how inhaled allergens and environmental pollutants affect the lungs.

In addition to his many accomplishments, Cook is also an adjunct assistant professor in the Department of Immunology at Duke University School of Medicine. (Photo courtesy of Steve McCaw)

Cook received his B.S. and Ph.D. in microbiology and immunology from McGill University in Montreal, and began his research career in 1990 under the tutelage of Nobel Laureate Oliver Smithies, D.Phil., at the University of North Carolina at Chapel Hill School of Medicine. As a postdoctoral fellow in Smithies lab, Cook co-authored several articles that appeared in prestigious journals, such as Science and Proceedings of the National Academy of Sciences.

When Cook completed his fellowship in 1996, he joined Schering-Plough Research Institute in Kenilworth, N.J., as an associate principal scientist, and quickly rose to the position of principal scientist. He left Schering-Plough to pursue an academic position as an assistant professor in the Division of Pulmonary, Allergy, and Critical Care Medicine at Duke University Medical Center in Durham, N.C. After four years at Duke, he joined NIEHS to head the Immunogenetics Group.

"I feel very honored because there are so many truly outstanding tenured investigators at NIEHS," Cook said, after hearing word of his tenure appointment. "I am grateful to the members of my laboratory for their hard work, and to many other people at NIEHS that have given me indispensable help and support over the past several years."

One of the people who advised Cook during his time at NIEHS is Anton Jetten, Ph.D., head of the Laboratory of Respiratory Biology. He noted that Cook's lung studies have helped broaden the knowledge of respiratory diseases, by identifying potential targets in the treatment of allergic asthma.

"Don's studies have significantly advanced our understanding of how environmental agents impact the cells and molecular pathways that orchestrate allergic responses in the lung," Jetten said.

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NIEHS awards Superfund occupational and safety training grants

By Sara Mishamandani

The NIEHS Superfund Research Program (SRP) welcomes the Harvard School of Public Health, University of Minnesota, and University of Washington as newly funded Occupational and Safety Training Education Programs on Emerging Technologies (R25) grantees.

"This research education program was developed to highlight SRP's interest in emerging technologies. We determined that there was a need for this type of training through interaction with the public, previous and current grantees, and our colleagues from the U.S. Environmental Protection Agency and Agency for Toxic Substances and Disease Registry," said Danielle Carlin, Ph.D., SRP program administrator.

"I am excited about adding a new program to the SRP grant portfolio, and I think this will be an excellent opportunity for professionals and graduate students to learn about emerging technologies in the workplace, and ultimately learn about safer practices when using these technologies," she continued.

Developing curricula on occupational health and safety

These SRP grants are awarded to institutes of higher education, to develop continuing education and academic curricula on occupational health and safety management practices in areas of emerging technologies, including emerging hazardous waste products, green chemistry, and sustainable remediation. The curricula will be available to industrial hygienists, graduate students, and other personnel involved in the evaluation, management, and handling of hazardous substances.

"Emerging technologies present new health and safety challenges," said Robert Herrick, S.D., lead researcher for the R25 grant at Harvard School of Public Health. "The education programs will help further the Superfund Research Program's aim of protecting workers from the effects of hazardous substances on human health."

The awards are also collaborative in nature. Applicants were encouraged to join forces with at least two other higher education institutions, to develop the emerging technologies curricula. These partnerships broaden the knowledge and experience available, to develop innovative materials for training a variety of audiences to work safely with emerging technologies.

"As a side benefit, the award will enhance our education and training activities on all workplace health and safety topics, not just with emerging technologies, because our program faculty will learn how to develop Web-based modules on their own that can be applied to other topics," said Peter Raynor, Ph.D., lead researcher for the University of Minnesota R25 grant.

"This new SRP education program will train the next generation of health and safety professionals in advanced and emerging technologies," said SRP Director Bill Suk, Ph.D. "The people using these new tools will do so in a way that improves their work life quality.

(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.)

"We are extraordinarily grateful to NIEHS for providing this opportunity," said Herrick. "With our academic partners at the Massachusetts Institute of Technology and Tulane University, we will develop a research education program that prepares professional practitioners and researchers in the evaluation, handling, and management of hazardous substances and conditions associated with emerging technologies." (Photo courtesy of Robert Herrick)

The Awardees

- Herrick and colleagues at the Harvard School of Public Health will create an education and training program in the management of hazards associated with emerging technologies, including nanotechnology, drug delivery in healthcare, and sustainable remediation. The program will prepare professional practitioners and researchers to evaluate, handle, and manage hazardous substances and conditions associated with these emerging technologies.

- At the University of Minnesota, Raynor's team will develop a comprehensive assortment of focused, Web-based modules, to train professionals, as well as undergraduate and graduate students, to work safely with engineered nanomaterials. The modules will be designed so that they can be used by instructors to tailor education and training initiatives on the health and safety of nanotechnology to serve the unique needs of different learners.

- Lead researcher Michael Yost, Ph.D., and colleagues at the University of Washington will focus on developing sustainable solutions to potential workplace health and safety risks associated with biotechnology, nanotechnology, alternative green chemistry, and green landscaping. The program focuses training efforts on identification and evaluation of potential health risks and environmental impacts. It will also concentrate on developing appropriate controls and substitution strategies for long-term sustainable technology solutions, to minimize potential harmful waste, reduce process hazards, and lower energy costs.

"Our partnership with the University of Iowa and Dakota County Technical College will help all three institutions to enhance our education and research activities," said Raynor. "Our research findings will be incorporated into our educational materials, and the development of the educational materials will lead to new research ideas on which we can work collaboratively." (Photo courtesy of Peter Raynor)

"Implementation of this training will provide broad awareness and knowledge in the workplace of appropriate application of sustainable technologies and alternative chemistries among personnel engaged in scientific discovery, process development, product engineering, and worker health and safety," said Yost. (Photo courtesy of Michael Yost)

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NIEHS welcomes Nanjing Medical University delegation

By Eddy Ball

When leaders of the Nanjing Medical University (NMU) School of Public Health (SPH) set out to advance the school's environmental health science curriculum, they decided to pursue a Memorandum of Understanding (MOU) with leading U.S. biomedical research centers at Harvard University, Johns Hopkins University (JHU), and, not surprisingly, NIEHS. The trip to North Carolina was part of the first visit to the U.S. for the postdocs and students in the delegation.

Even before the 16 NMU scientists, administrators, and trainees made their visit to NIEHS July 24, the day after signing an MOU with the JHU Bloomberg School of Public Health, they surely anticipated finding common ground with NIEHS scientists. But the Chinese scientists may not have expected to discover a near mirror image of their own goals, as presented in opening remarks by Dean of NMU SPH Feng Chen, Ph.D., reflected in a presentation by NIEHS Scientific Director Darryl Zeldin, M.D., on the Institute's strategic plan.

Organizations with much in common

"There are such strong similarities and shared interests in various aspects of both toxicology and environmental health, between the two organizations," said lead researcher Kenneth Korach, Ph.D., head of the NIEHS Laboratory of Reproductive and Developmental Toxicology. Korach made the initial contact with NMU during a visit to Nanjing in 2011, when he spoke with then SPH Dean Hongbing Shen, M.D., Ph.D., who is now NMU vice president for research.

Chen, left, shook hands with JHU Bloomberg School of Public Health Dean Michael Klag, M.D., after signing an MOU between NMU and JHU July 23 in Baltimore. (Photo courtesy of JHU).

According to Korach, the fit is a good one between the leading U.S. environmental health sciences research center and the highly rated Chinese medical university. "These are individuals who are very research science oriented," Korach said of his NMU colleagues. "They had trained in the U.S., and they are obviously very interested in increasing the stature and position of Nanjing."

Korach said he expects NMU and NIEHS to finalize their MOU in the near future, increasing collaborations and training opportunities for NMU graduate students, fellows, and junior scientists, possibly during a future visit to China by Korach and Zeldin.

Korach, above, talked further with Xia, during Xia's visit to the U.S. Environmental Protection Agency in Research Triangle Park, N.C., in early 2011. (Photo courtesy of Steve McCaw)

A plan to share research and training resources

Presenters Zeldin and Korach were joined by other leading scientists at NIEHS, including John Bucher, Ph.D., associate director of NTP; Dale Sandler, Ph.D., head of the Epidemiology Branch (EB); Hugh Tilson, Ph.D., editor in chief of Environmental Health Perspectives; Allen Wilcox, M.D., Ph.D., head of the EB Reproductive Epidemiology Group; Stephanie London, MD., Dr.P.H., head of the EB Genetics, Environment, and Respiratory Disease Group; and David Umbach, Ph.D., a staff scientist in the Biostatistics Branch.

The lead researcher in the delegation was Yankai Xia, M.D., Ph.D., head of what the Chinese call a Key lab, established with targeted national government funding at NMU. His research interests combine epidemiology, especially birth cohorts and common birth defects studies, with stem cell toxicology, and developmental and reproductive toxicology. Xia and others in the delegation expressed special interest in NIEHS work with large cohorts in the area of molecular epidemiology, such as the GuLF STUDY and Sister Study.

Following the program, the visitors enjoyed a tour of the Institute lead by John Schelp, special assistant for community engagement and outreach in the NIEHS Office of Science Education and Diversity.

The day after their visit to NIEHS, the NMU delegation took advantage of their proximity to Cary, for a visit to scientific software leader SAS, which had a special appeal for Chen and several others in the delegation who are biostatisticians with interests in big data analysis.

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Balbus facilitates IOM webinar series

By Audrey Pinto

NIEHS Senior Advisor for Public Health John Balbus, M.D., played a leading role in a three-part webinar series this summer on global health and sustainable development, moderating and providing opening comments.

As NIEHS program lead for the Institute of Medicine (IOM) Roundtable Innovation Collaborative, Balbus facilitated the webinar series. The webinars were co-sponsored by NIEHS and the Pan American Health Organization and hosted by the Institute of Medicine's (IOM) Roundtable on Environmental Health Sciences, Research, and Medicine.

NIEHS continues to build a global presence

In 2012, IOM and NIEHS launched the Global Environmental Health and Sustainable Development Innovation Collaborative, with the intention of bringing together a global community of stakeholders to develop novel economic frameworks and science-based indicators, and to consider their implications for policymakers.

Since launching the NIEHS-IOM joint program, Balbus has contributed to NIEHS efforts to strengthen its global presence, with webinars in the winter of 2012 that focused on the development of a new agenda for the world, as the United Nations (U.N.) Millennium Development Goals (MDGs) reach their target date of 2015.

Each of this summer's webinars brought together an international panel of environmental health and economic experts from academia, government and nongovernment organizations, and professional societies, in a dialogue around health, economic development, equity, sustainability, and environmental challenges, with the goal of stimulating new solutions for future generations.

Balbus is a principal of the U.S. Global Change Research Program, leading NIEHS efforts on climate change and human health. (Photo courtesy of Steve McCaw)

Looking at new indicators to determine sustainability

At the opening of the first webinar May 23 on Health in the Context of Sustainable Economic Frameworks, Balbus noted that the economic health of a nation is usually measured by its gross domestic product (GDP). "But, of late, there has been interest in going beyond GDP and using other indicators," he said. Three speakers proposed several new indices, including measures of both mental and physical well-being, as well as the human health impact of environmental exposures and risk.

With the second webinar June 27 on Health in the Context of Global Climate Change, Balbus introduced the topic of developing credible scenarios for predicting future health effects of climate change. He pointed out that to understand how climate change will affect future generations, we must first understand what the future world will look like. "We have to improve the models we use," Balbus explained, "and we have to be able to produce rigorous and credible scenarios of the future to support these predictive efforts and these models."

The speakers then outlined a set of shared socioeconomic pathways that are being developed to aid in the modeling and analysis of climate change mitigation and adaptation, and suggested ways of disseminating information on these climate change scenarios.

In the final seminar July 25 on Health in the Context of U.N. Processes to Develop Post-2015 Goals and Sustainable Development Agenda, three speakers outlined recommendations for going beyond the MDGs set for 2015 and discussed opportunities to inform the global community on health information for decision-making and to raise awareness of the health implications.

The discussions included integrating the role of health in a broader context in the post-2015 MDGs, emphasizing the importance of universal health coverage, linking potential indicators of health and sustainability to reflect policies that enhance sustainability and improve health, and improving the possibility of greater resilience of populations to adverse environmental conditions.

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

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Duke SRP uses blog to explain research projects

By Sara Mishamandani

This summer, the Duke University Superfund Research Program (SRP) has ramped up postings on its blog, ToxInsider, to explain NIEHS-funded research findings and provide insights into scientific research from trainees.

"The blog is a great way to make more information about Duke SRP environmental health research accessible to those who don't really have a science background," said Gretchen Kroeger, Duke SRP Research Translation Core (RTC) member who leads the blog project. "As communicating research to a variety of audiences becomes more important for a young scientist, getting interns to write blog posts is a great way to teach science communication while kick-starting our blog."

Shown left to right are Savannah Volkoff, Gretchen Kroeger, and Noelle Wyman, members of the Duke SRP RTC and contributors to the blog. (Photo courtesy of Gretchen Kroeger)

Clarifying scientific concepts for a general audience

Duke SRP's focus is on how exposure to chemicals early in life may impact development and lead to health issues later in life. The SRP scientists study how pesticides, flame retardants, polycyclic aromatic hydrocarbons (PAHs), and nanocompounds impact brain development, behavior, thyroid function, and more.

In July, new posts included Exposing Nemo; What doesn't kill you makes you stronger. True for fish, too?; Are there flame retardants in health care settings?; and Country Roads — all written with a personal touch by Duke SRP interns and graduate students. Interns discuss their personal experiences at Duke, while explaining difficult scientific concepts.

"We are hoping to reach out to people at Duke who may not know about us or our research," said Noelle Wyman, another Duke RTC member. "When we post something on Facebook from our blog, we also get a spike in traffic to the rest of our website, increasing our exposure outside the Duke SRP community," said Kroeger.

Volkoff, right, sorted mummichogs on a recent research field trip to the Elizabeth River in Southern Virginia. Volkoff, a recent graduate of San Francisco State University in California, has been working with the Duke RTC and developed the idea for the Friend Request Accepted series. She has also written several blog posts throughout the summer and will continue the project into the fall. (Photo courtesy of Gretchen Kroeger)

Explaining model organisms

In an effort to familiarize readers with organisms studied in Duke SRP labs, the blog also began a Friend Request Accepted series. Just as Facebook provides an opportunity to expand networks, stay in contact with people, and get to know them better, these Facebook-inspired posts introduce some of the model organisms used in research projects at Duke SRP.

Part I of the "Friend Request Accepted" series features the mummichog, a model organism used to research mechanisms of PAH toxicity at Duke. Part II highlights the model organism *C. Elegans*, and part III explains the use of the Sprague Dawley rat to explore the impacts of chemical exposure.

"One of the great things about the Friend Request Accepted posts is that the general public doesn't typically understand how a worm or a mouse study can relate to human health," said Wyman. "This series helps clarify how we can use model organisms to better understand human and ecosystem health in a way that makes sense to a general audience."

Volkoff, left, and Kroeger, right, described their sampling trip to the Elizabeth River in their June blog post, Mummichogs and Milkshakes. (Photo courtesy of Gretchen Kroeger)

Disseminating relevant SRP research

Duke SRP publicizes its blog on Facebook and Twitter. The Duke SRP lab, led by Richard Di Giulio, Ph.D., also maintains a Twitter account for Casper the Mummichog, with additional information about Duke SRP research and events.

"We also want to provide information that relates general themes of Superfund research to environmental issues we hear about in the news," said Wyman. "Social media is a great way for us to network and share information with people who may care about these issues but wouldn't otherwise ever see our website."

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

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Iowa SRP hosts health science and engineering summer camp

By Sara Mishamandani

High school students from across the country gathered at the University of Iowa (UI) in July to explore various environmental health topics and learn more about scientific research at a week long summer camp. The UI Superfund Research Program (ISRP) hosted the camp for 20 students, focused on the sources, remediation, and human health impacts of polychlorinated biphenyls (PCBs).

Craig Just, Ph.D, and Melissa Ward of the ISRP Community Outreach Core (COC) taught a course on engineering and health science that explored real-world problems related to human health and environmental clean up.

"One of the aims of the ISRP COC and Research Translation Core (RTC) is to improve scientific literacy in junior high and high school students," said Ward. "ISRP has been involved in this camp for the past three years and the students always love learning about the complexities of a real-world problem."

The students toured the UI campus environmental health laboratories and even had the opportunity to watch a mouse necropsy. They also worked on many design challenges throughout the week, including a four-story egg drop challenge.

Students learned about the multidisciplinary nature of ISRP science, met researchers, and had the opportunity to learn about environmental health research firsthand. (Photo courtesy of Melissa Ward)

PCB contamination in the Indiana Harbor

Students focused on the issue of PCB contamination and remediation in the Indiana Harbor and Ship Canal, the site of the ISRP study on exposures to airborne PCBs. Students worked in small research teams to explore various approaches for remediating the Indiana Harbor and Ship Canal, which contains sediments contaminated with toxic industrial chemicals. The business leaders in the community say the sediments must be dredged to enable a more productive ship passage. However, residents living near the canal fear they will be exposed to harmful chemicals, including PCBs, that could be released when the sediments are disturbed. A team of health scientists and engineers are involved in this project at ISRP (see story).

Students split into small research teams, to complete problem-solving exercises and learn more about the engineering and health science aspects of PCB contamination and clean up. (Photo courtesy of Melissa Ward)

During the camp, students had the chance to work on both sides of the dredging scenario — as a health scientist and as an engineer. With hands-on exercises in environmental sampling, laboratory analysis, engineering design, and team building, students learned ways to approach the real-world problem. They then created scientific posters highlighting what they learned about PCBs. Posters were presented to the group, as part of a student poster competition. The winning poster team presented its work to students, families, and staff at the camp's closing ceremonies.

"This camp has been a great extension of our engagement work in Columbus Junction, Iowa, and East Chicago, Indiana," said Just. "The superintendent of the Columbus Community Schools came to the camp's closing ceremony a couple of years ago and shared pictures with his staff. It was a proud moment for him."

"Many students leave our program saying that the curriculum has helped inform their future college and/or career choices in either the health sciences or engineering," said Ward.

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

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Science Notebook

Birnbaum lab premieres publication on flame retardant additive

By Sheila Yong

About a year and a half after the start of its operation, the Laboratory of Toxicology and Toxicokinetics (LTT), headed by NIEHS and NTP Director Linda Birnbaum, Ph.D., showcased its first publication on hexabromocyclododecane (HBCD), an additive flame retardant primarily used in polystyrene foam building materials (see story). The commercial mix of HBCD consists of three stereoisomers — alpha, beta, and gamma, with gamma making up 70-80 percent of the mixture.

Sanders is a former researcher with NTP and a longtime colleague of Birnbaum. (Photo courtesy of Steve McCaw)

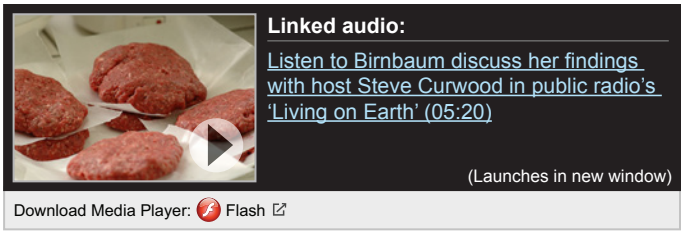
The study, published in the August issue of Toxicological Sciences, focuses on beta-HBCD and its effects on female laboratory mice. LTT is a small team, guided by Mike Sanders, Ph.D., lead author of the study.

Prior to establishing LTT, Birnbaum, a board-certified toxicologist, spent several years researching the toxic effects of flame retardants. "I'm especially interested in the brominated flame retardants (BFRs)," said Birnbaum. "They are the most widely used, because they are cheap and extremely effective in reducing fire-related injury and property damage."

Birnbaum said that these chemicals have come under intense scrutiny over the years, because of their potentially harmful effects to the environment and human health. That's why LTT made the study of BFRs its primary focus when it was first founded.

Unraveling the beta isomer mystery

HBCD is a type of BFR that is mixed with the product matrix, rather than being chemically bound. As a result, it escapes easily into the environment. A survey conducted by Birnbaum and colleagues in 2012 found detectable levels of HBCD in 42 percent of food samples from supermarkets in Dallas, Texas. *In vitro* studies have also shown HBCD to be an anti-androgen and aromatase inhibitor, specifically binding to several steroid hormone receptors.



While extensive toxicokinetic studies have been done on the alpha and gamma isomers of HBCD, toxicology data for the beta isomer is lacking and the implications of exposure are unknown. Therefore, the aim of this study is to obtain comparative kinetics data for the beta isomer, which can be used to support toxicological evaluations and risk assessment of HBCD isomeric mixtures.

The study utilized the same mouse line used in previous studies on the alpha and gamma isomers, to enable an accurate comparison of the exposure effects for all three isomers. The researchers found that, while most of the beta-HBCD given to the mice was excreted within a four-day period, there were still measurable amounts of the chemical accumulated in these animals, particularly in the liver and fat tissues. Higher treatment doses resulted in higher tissue accumulation, especially in the fat tissue, which showed about three-fold higher accumulation for treatment doses of 30 and 100 milligrams per kilogram, compared to 3 milligrams per kilogram. Logically, repeat-dose treatment also led to higher tissue accumulation compared to single-dose treatment.

Birnbaum is the first toxicologist to serve as director of NIEHS and NTP. (Photo courtesy of Steve McCaw)

Comparison among the alpha, beta, and gamma isomers

The study concluded that, like gamma-HBCD, beta-HBCD is extensively metabolized and is less likely to accumulate in the tissues compared to the alpha isomer. This finding may explain why alpha-HBCD is the most prevalent isomer found in the biota, including plants, animals, and even blood and breast milk, among populations living in areas exposed to high levels of HBCD.

Unfortunately, beta-HBCD is far from being safe. The current study reports that a measurable portion of the beta-HBCD was converted to the gamma isomer in the treated mice. Previous research by Birnbaum and colleagues has shown that the gamma-HBCD also undergoes rapid stereoisomerization to the alpha and beta isomers. Since both the beta and gamma isomers can potentially be converted to alpha-HBCD, the ultimate outcome could be an even higher alpha-HBCD accumulation in organisms exposed to the chemical.

The LTT is located at NIEHS, but is funded by the National Cancer Institute.

Citation: Sanders JM, Knudsen GA, Birnbaum LS. 2013. The fate of beta-hexabromocyclododecane in female C57BL/6 mice. Toxicol Sci 134(2):251-257.

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

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Metabolomics symposium highlights the field's triumphs and challenges

By Heather Franco

Wouldn't it be easier to fish using explosives instead of a hook and line? Keynote speaker Ian Wilson, Ph.D., of the Imperial College London, used that very metaphor to describe large-scale omics searches for early biomarkers of disease, at the start of the Aug. 9 symposium on metabolomics platforms.

"People call metabolomics fishing," Wilson joked, "but I say that I fish with hand grenades."

In her opening comments, Susan Sumner, Ph.D., organizer and host of the National Institutes of Health (NIH) Eastern Regional Comprehensive Metabolomics Resource Core (RCMRC) Symposium at RTI International headquarters in Research Triangle Park, N.C., offered a more straightforward definition for the audience, which included a number of scientists from NIEHS.

"Metabolomics involves the broad-spectrum analysis of the low molecular weight complement of cells, tissues, and biological fluids," explained Sumner, who is director of the RTI RCMRC. "It allows us to determine the pattern of changes in the related metabolites arising from any disease, dysfunction, disorder, or exposure."

Sumner described the metabolic profiling program that she oversees as part of the RTI RCMRC Pilot and Feasibility Program. The program requires recipients of pilot and feasibility grants to make their data publicly available. (Photo courtesy of Steve McCaw)

A love-hate relationship with metabolic analysis platforms

Wilson gave a rousing address on "How NOT to do Metabolic Profiling," with a focus on the metabolic techniques that he has used for years. He described his experiences with nuclear magnetic resonance (NMR) and liquid chromatography-mass spectrometry (LC-MS).

"NMR is like a mother that is reliable and doesn't lie to you, but is often insensitive," he joked. "LC-MS is like a lover that lies to you." According to Wilson, the trick is to turn LC-MS into a trusted partner, through the use of quality controls.

Despite its drawbacks, Wilson believes LC-MS can be an efficient and sensitive technique. As he explained with yet another attention-getting metaphor, "LC-MS includes everything, which means you see everything. Thus, the challenge is to take oceans of data, and make rivers of information, and finally puddles of knowledge."

With his dry wit and often self-deprecating humor, keynote speaker Wilson kept everyone in the audience laughing, as he described his triumphs and failures in metabolic research over the years. (Photo courtesy of Steve McCaw)

NIH program supports the development of metabolomics

The RTI RCMRC is one of three cores funded by the NIH Common Fund, to establish national standards, increase the national capacity to provide metabolic profiling and data analysis, and facilitate institutional development of research, training, and outreach.

Sumner described the RTI core's pilot and feasibility study program, highlighting research performed with Richard Loesser, M.D., of Wake Forest University, to determine biomarkers important in development and progression of osteoarthritis. Sumner also described the RTI core's internship program, and the NIH funded metabolomics training programs at the University of North Carolina at Chapel Hill directed by Martin Kohlmeier, M.D., and University of Alabama at Birmingham with Stephen Barnes, Ph.D.

In a second talk about work at the RTI core, James Raymer, Ph.D., an analytical chemist, described the development and use of gas chromatography-mass spectrometry (GC-MS) in metabolic profiling for environmental health studies (see text box).

The daylong program also included talks by scientists from industry groups about the use of two-dimensional gas chromatography-mass spectrometry (GCxGC-MS) and the applications of metabolomics in agricultural research.

Symposium opens avenues for NIEHS scientists

NIEHS scientists attended the symposium to learn about metabolomics and how to apply it to their research. As Environmental Genomics Group fellow Mehmet Karaca, Ph.D., explained, "The symposium made me appreciate how using proper metabolomics analysis, it is possible to catch the differences in seemingly similar biological samples." Honglei Chen, M.D., Ph.D., lead researcher and head of the Aging and Neuroepidemiology Group, said, "I found the discussions about technology and quality control very useful."

Thus, the symposium achieved its goal of facilitating future metabolomic studies. As Carl Bortner, Ph.D., director of the NIEHS Flow Cytometry Center, observed, "It is clear to me that as this technology continues to move forward and becomes more advanced, the detection of metabolites in many different types of samples will lead to great discoveries in science."

The symposium highlighted the many challenges that metabolic profilers face. As Leesa Deterding, Ph.D., right, director of the NIEHS Collaborative Mass Spectrometry Support Group, explained, "In biomarker discovery, the difficulty is in discovering and identifying a compound that is relevant to the biological question." (Photo courtesy of Steve McCaw)

Ecometabolism — new directions in toxicology research?

At the RTI RCMRC, Raymer and colleagues are using metabolic profiling to discern changes in metabolites in various disease and exposure models, termed ecometabolomics. They are currently working on three projects and hope to collaborate with additional environmental scientists.

Effect of climate change on mayfly metabolism

In collaboration with David Buchwalter, Ph.D., at North Carolina State University, Raymer subjected mayflies to hypoxia and heat challenges. GC-MS analysis was able to separate the groups and identify metabolites potentially involved in adaptive responses.

Using exhaled breath to study respiratory disease

Using an RTube, vapors and aerosolized drops from exhaled breath were condensed for GC-MS analysis. Samples have been collected from patients with asthma, chronic obstructive pulmonary disease, and cystic fibrosis, and are being analyzed for comprehensive discovery investigation.

Analyzing the impact of particulate matter on human health

Particulate matter (PM) represents a public health concern, as it has been linked to asthma and cardiovascular disease. Currently, two projects are underway using GC-MS to assess the impact of PM exposure on human health. One study assesses the effect of wood smoke exposure on the development of asthma in children. The other determines the impact of PM exposure in a controlled chamber in adults.

Jack Cochran, from chromatography manufacturer Restek, delivered an informative lecture on the development and applicability of GCxGC-MS in metabolomics. (Photo courtesy of Steve McCaw)

Raymer described how his group at RTI is utilizing GC-MS to study ecometabolomics, with direct applications for environmental health science research. (Photo courtesy of Steve McCaw)

While the symposium primarily focused on mass spectrometry, Eugene DeRose, Ph.D., manager of the NIEHS NMR Center, hopes to use NMR in conjunction with mass spectrometry to study metabolomics at NIEHS. "At the present time, the NMR laboratory at NIEHS is not involved in metabolomics research, but the symposium gave me valuable information of what might be required if NIEHS researchers decide that they want to use NMR in metabolomic studies," he explained. (Photo courtesy of Steve McCaw)

(Heather Franco, Ph.D., is an Intramural Research Training Award fellow in the NIEHS Laboratory of Reproductive and Developmental Toxicology Reproductive Developmental Biology Group.)

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Trainees' research recognized at SSR annual meeting

By Eddy Ball

Work by three trainees in the NIEHS Reproductive Developmental Biology Group (RDB) won top honors at the Society for the Study of Reproduction (SSR) meeting July 19-23 in Montreal.

Visiting predoctoral fellow Chang Liu, a graduate student at the University of Illinois at Urbana-Champaign, and Intramural Research Training Award fellows Erica Ungewitter, Ph.D., and Heather Franco, Ph.D., were among the 16 winners of the Lalor Foundation Merit Award, which includes a prize of $500.

Along with their Lalor awards, Liu and Ungewitter also won SSR Trainee Research Awards. Liu placed first in the oral category, winning an additional $500 prize, and Ungewitter took second place in the poster category, receiving an extra $300.

"These trainees really made me and NIEHS look great at the meeting," said Humphrey Yao, Ph.D., head of the RDB and mentor of the winners. "I appreciate the support of the intramural program that allowed us to attend the meeting."

According to Yao, the selection process for the Trainee Research Award is very stringent, involving the selection of six finalists for each category — best platform (oral) presentation and best poster presentation — from around 900 abstracts submitted by predoctoral and postdoctoral fellows. External reviewers cull for the top 200, and the award committee then chooses the final six oral and six poster finalists. Judging criteria include merit of the study, presentation format, delivery, visual aids, and response to questions during discussion.

Quality mentoring translates into award-winning research presentations

While the award winners are exceptionally talented young scientists, Liu, Ungewitter, and Franco also credit Yao's mentoring and their career development experiences in the NIEHS Laboratory of Reproductive and Developmental Toxicology (LRDT) with helping to make the awards a reality.

Liu, who has worked in the group for the past four years pursuing a Ph.D. in reproductive biology, said he appreciated the support and direction Yao has provided. "Humphrey is always available and always encouraging. He is good at building up your confidence, cheering you up when you're low, and motivating you to move on with your research projects," Liu said.

The winners also benefited from structured training experiences provided by LRDT, which is headed by Kenneth Korach, Ph.D. "LRDT has a summer fellows' seminar series, where all the trainees present research and are rated by the other scientists in LRDT," Korach explained.

The ratings cover subject matter and organization, as well as presentation skills, and colleagues offer specific recommendations about how to improve. "This kind of practice helps in many ways when the fellows go to national meetings," Korach said.

Award-winning research from RDB

Working with mouse models, members of the Yao group investigated the developmental differentiation of stem and progenitor cells in the reproductive system of mammals, for insight into the mechanism of the process and the ways early-life events could result in abnormalities that develop later in life.

- **Liu C**, Yao HH-C. 2013. Unveil the Origins of Theca Cells: Divergent Sources to a Convergent End. Meeting abstract 1.

  Theca cells play essential roles in normal ovarian function yet their origin remains unclear. These lineage-tracing studies investigated whether somatic progenitor cells in the gonad (*Wt1*-positive) and/or mesonephros (*Gli1*-positive) contribute to the theca cell lineage. The studies uncovered multiple origins for the progenitors of the theca cell lineage — the gonadal *Wt1-positive* cells and the extragonadal Gli1-positive cells. The experiments also demonstrated that these two sources of theca progenitor cells are indispensable for normal ovarian function.

- **Ungewitter EK**, Lichti-Kaiser K, Jetten AM, Yao HH-C. 2013. GLI-similar 3 is a Sexually Dimorphic Regulator of Fetal Germ Cell Development in the Mouse. Meeting abstract 453.

  This study traced genes involved in embryonic sex determination, focusing on the first stage of meiosis, a special type of cell division necessary for sexual reproduction. The findings suggest that *Glis3* is critical for germ cell development and maintenance in the testis and that it does so by preventing male germ cells from entering meiosis prematurely through a novel pathway independent of retinoic acid, which is able to induce meiosis in female germ cells.

- **Franco HL**, Tsai M-J, Tsai SY, Yao HH-C. 2013. The Novel Regulation of Both Male and Female Murine Reproductive Tract Regression by COUP-TFII. Meeting abstract 28.

  This investigation of the factors that govern embryonic reproductive tract development tested the hypothesis that the orphan nuclear receptor COUP-TFII plays a critical role in the process. Surprisingly, ablation of COUP-TFII resulted in the presence of two reproductive tracts in both males and females, making this the first model whereby a genetic alteration causes a failure of ductal regression in both sexes, and opening avenues for future research into the mechanisms of reproductive tract development.

For Yao, the awards were also a symbolic passing of the torch. In 1999, as a graduate student at one of his first SSR meetings, Yao won a first place Trainee Research Award for his oral presentation, setting the tone for a career that took him to the University of Illinois at Urbana-Champaign, where he was an associate professor, and then on to NIEHS. According to Yao, SSR is especially nurturing for students and fellows, with approximately 70 percent of the presentations at each year's annual meeting being given by trainees.

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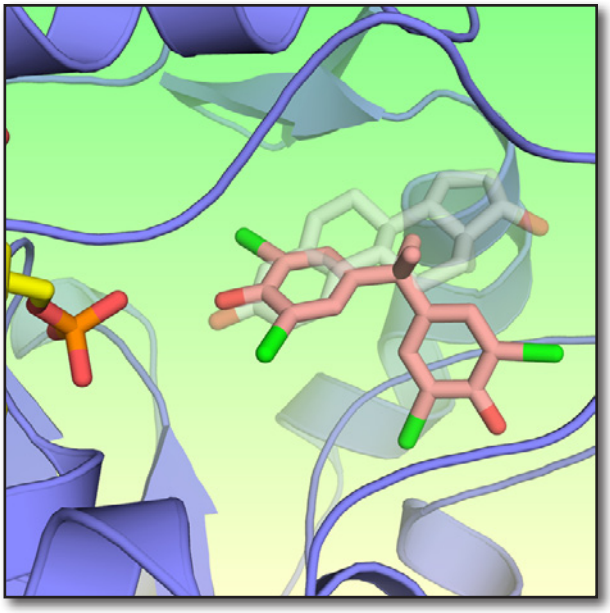
"All of Humphrey's projects are the type answering important questions that not many people have tried to answer, but are needed in order to move the field forward," Korach said of the group's work. "Humphrey has recruited very, very well." Shown above, from left, are the award winners and their mentor — Ungewitter, Yao, Liu, and Franco. (Photo courtesy of Steve McCaw)

3-D images show flame retardants can mimic estrogens

By Robin Mackar

By determining the three-dimensional structure of proteins at the atomic level, a new study by NIEHS researchers shows how some commonly used flame retardants, called brominated flame retardants (BFRs), can mimic estrogen hormones and possibly disrupt the body's endocrine system. BFRs are chemicals added or applied to materials to slow or prevent the start or growth of fire.

"We're beginning to have a better understanding of flame retardants and their effect on human health. This particular study helps us literally see what brominated flame retardants do when they get in the body — they interfere with the body's natural hormones," said Linda Birnbaum, Ph.D., director of NIEHS and NTP. "Using the 3-D imaging capabilities, we can see the flame retardants binding, or attaching, to proteins like estrogens do."



The brominated flame retardant TBBPA is shown, in this 3-D image, binding to the active site of an estrogen metabolizing enzyme (pink), interfering with the body's natural release of estrogen (transparent grey).

Birnbaum is an author on the new study which appears online in Environmental Health Perspectives. She and her fellow researchers conducted the study in a facility jointly supported by several NIH institutes.

Birnbaum, a leading researcher on flame retardants, joined with biologists and a postdoctoral fellow to look more closely at one of the most widely used BFRs, tetrabromobisphenol A (TBBPA). Earlier this year, NTP released data from a two-year bioassay study, showing that TBBPA caused tumors in rats and mice.

“Having chemicals act like estrogen or other hormones disrupts how the endocrine system works,” said Birnbaum. “In this case, the ability of flame retardants to bind to and inhibit an enzyme that metabolizes estrogen, called estrogen sulfotransferase, could result in the body having too much estrogen.”

The endocrine system is one of the body’s main communication networks and is responsible for controlling and coordinating numerous functions, including growth and development, reproduction, response to stress, and energy levels.

There are hundreds of different flame retardants. They are often broken into categories based on chemical structure and properties. BFRs, such as TBBPA, are used in many types of consumer goods, including electronics, furniture, building materials, and automobiles. Flame retardants are being studied, because of their pervasiveness and concerns about possible adverse effects on the endocrine, immune, reproductive, and nervous systems.

For this study, the researchers used X-ray crystallography to build a 3-D model of the protein binding to flame retardants. Crystallography allows researchers to look at proteins at the atomic level. They examined how TBBPA and a metabolite, or derivative, of another flame retardant called tetrabromodiphenyl ether, or BDE-47, compared with binding of estradiol, a naturally occurring estrogen, to the estrogen sulfotransferase.

Although many flame retardants, including BDE-47, are no longer produced in the United States, some BFRs are slow to break down and can persist in the environment. People can be exposed to flame retardants through a variety of ways, including diet; consumer products in the home, car, and workplace; and house dust.

“Using crystallography allows us to visualize exactly how these compounds can interact with the body’s enzymes,” said Lars Pedersen, Ph.D., Collaborative X-ray Crystallography Group leader at NIEHS. “Our results revealed TBBPA binding to the estrogen sulfotransferase at the same position and in a similar manner as estradiol binds.”

“Although there is much more to be learned about how these chemicals and their metabolites impact different systems in the body, every piece of the puzzle helps increase our understanding of the effects they may have.” Researchers, like Pedersen and Birnbaum, hope the findings will be used by companies to develop safer alternatives to current flame retardants.

Citations:

Gosavi RA, Knudsen GA, Birnbaum, LS, Pedersen LC. 2013. Mimicking of estradiol binding by flame retardants and their metabolites: a crystallographic analysis. Environ Health Perspect; doi:10.1289/ehp.1306902 [online August 19, 2013]

National Toxicology Program. 2013. Tetrabromobisphenol A. Available: http://ntp.niehs.nih.gov/go/TS-M200033 [accessed August 19, 2013].

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

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Study finds wide range in pregnancy length

By Monica Frazier

Researchers in the NIEHS Epidemiology Branch found a much broader range in the length of human pregnancies than is usually considered average. Their results, published Aug. 6 in the journal Human Reproduction, could lead to a different way of assigning due dates to pregnancies in the future.

The authors found that the median time from ovulation to live birth was 268 days, or 38 weeks, 2 days, but that this time ranged from 208 to 284 days. Most surprising was the 37-day range of gestational length among term births within a relatively select group of otherwise healthy, normal births. These findings were based on the study of 125 pregnancies from the North Carolina Early Pregnancy Study.

Jukic said of the Early Pregnancy Study used for this research, "[It] has been making solid contributions to the understanding of reproduction for almost thirty years." She added that the same study could be used to answer additional research questions that could benefit prenatal care methodology. (Photo courtesy of Steve McCaw)

A novel detection method

One fundamental problem that has historically plagued pregnancy length studies is the inability to accurately determine when gestation began. Physicians typically use a combination of the onset of the woman's last menstrual period and ultrasound measurements to determine a pregnancy's due date.

In this study, for the first time, levels of hormones found in daily urine samples were used to determine when the subjects ovulated. By accounting for cases where medical interventions were used to shorten the length of pregnancy, the researchers were able to determine a range of gestation lengths in normal births.

Anne Marie Jukic, Ph.D., the lead author on this publication and a postdoctoral fellow in the Reproductive Epidemiology Group headed by Allen Wilcox, M.D., Ph.D., said the results were surprising.

"We know that length of gestation varies among women, but some part of that variation has always been attributed to errors in the assignment of gestational age," Jukic explained. "Our measure of length of gestation does not include these sources of error, and yet there are still five weeks of variability. It's fascinating."

Unique rates of development

The fact that normal pregnancy can have such a wide range in length suggests that development rates are individualized. Indeed, the researchers found that the length of a pregnancy tends to correlate with other pregnancy lengths from the same woman, supporting this notion.

In addition to the start of ovulation, the number of days between fertilization and implantation was determined using the rise in the level of the hormone human chorionic gonadotropin. It was found that the longer the time between fertilization and implantation, the longer the gestation tended to be.

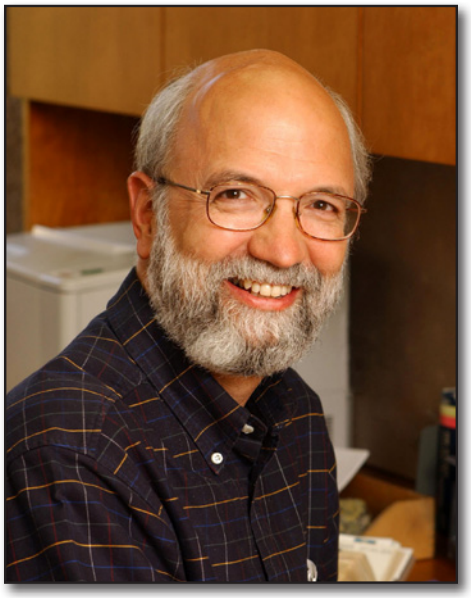
In addition, later rises in the hormone progesterone were associated with nearly two weeks shorter gestations than those with an early rise. These findings could indicate that each pregnancy has an intrinsic developmental pace.

There is potential that this study, and future studies, could be used to change the way obstetricians assign a due date for pregnancies. Jukic suggested that a range of dates may be better used for physicians, as many women who reach their assigned due date are often distressed if that date passes.

"Given the variability we saw in our data, it does seem appropriate to give women a range of dates in which they have a certain probability of delivering."

Co-author Donna Baird, Ph.D., leader of the Women's Health Group in the Epidemiology Branch, provided expertise in reproductive biology and endocrinology to the study. (Photo courtesy of Steve McCaw)

Clarice Weinberg, Ph.D., head of the Biostatistics Branch and a co-author on the study, has designed and overseen analysis of the Early Pregnancy Study's data collection since its origin. (Photo courtesy of Steve McCaw)



Wilcox was corresponding author on the paper. (Photo courtesy of Steve McCaw)

Citation: Jukic AM, Baird DD, Weinberg CR, McConnaughey DR, Wilcox AJ. 2013. Length of human pregnancy and contributors to its natural variation. Hum Reprod; doi:10.1093/humrep/det297 [Online 6 August 2013].

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

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DNA glycosylases in action — the search for damaged bases

By Raj Gosavi

Microbiologist and cancer researcher Susan Wallace, Ph.D., described her latest findings on how DNA glycosylases locate and repair damaged substrates, a process that may ultimately affect cancer susceptibility and carcinogenesis, in a talk Aug. 5 at NIEHS.

Aptly titled "DNA glycosylases search for and destroy oxidized DNA bases," Wallace's presentation explored the routine, endogenous production of oxidized DNA damage or lesions by exposure to radiation, inflammation, or chemical agents that happens six to ten thousand times each day. Most endogenous damages are effectively removed by a repair process called base excision repair.

Wallace is a distinguished professor and chair of the Department of Microbiology and Molecular Genetics at the University of Vermont (UV). She has received many honors for her work in the fields of cancer and molecular biology, has authored more than 170 publications and book chapters, and is currently an associate editor of the journals DNA Repair and Molecular Cancer Research.

Wallace set the tone for her talk, with a comment designed to underscore the importance of her field of study. "Fortunately, we have a well-functioning base excision repair pathway," she said. "Otherwise we all wouldn't be sitting here today."

NIEHS postdoctoral fellow Deepa Singh, Ph.D., above, hosted the talk on behalf of the Laboratory of Molecular Genetics Trainees' Action Committee. In her introduction, Singh remarked that Wallace was a good mentor, and took great interest in the career and professional development of graduate students and postdoctoral fellows in her lab. (Photo courtesy of Steve McCaw)

Lesions worth repairing

Wallace's research focus is to understand basic principles of how DNA glycosylases scan, recognize, and process their substrates, using a combination of techniques, such as enzyme kinetics and X-ray crystallography. By better understanding this critical process in the survival of the organism, she is searching for insights into how and why it goes wrong, and, conceivably, some way to help get repair back on the right track.

The base excision repair pathway is central in repair of these oxidized DNA lesions. The first step in this crucial pathway is where DNA glycosylases come into play. As Wallace explained, DNA glycosylases search for lesions and, once found, they kink the DNA, flip the lesion into the active site, and cleave the glycosyl bond.

Wallace, who has been consistently funded by the National Cancer Institute, has made significant contributions to biomedical science and, specifically, the field of radiation research (see UV feature story) for over four decades. (Photo courtesy of Steve McCaw)

Bacteria to human

One interesting aspect of Wallace's studies involved DNA glycosylases from plants, fungi, and vertebrates, because the key proteins do not function quite the same way in bacteria, yeast, or nematodes. Studying the similarities and differences among these glycosylases was important in providing some insight into their substrate specificities. Bacteria primarily use the Fpg family of proteins to remove 8-oxoguanine lesions, with the help of a region on protein called lesion recognition loop. Analogous glycosylases from plants (Fpg-like) and mammalians (NEIL1) have this region missing and consistently did not recognize the 8-oxoguanine lesions on DNA.

Wallace noted that NEIL2 and NEIL3, two other Fpg-like proteins in mammals, had even more diverse characteristics. Both preferred lesions in single-stranded DNA, because they lacked a couple of residues that are important in flipping the lesion bases out of the duplex DNA.

In the process of understanding the nature of broad substrate specificity of glycosylases, Wallace used crystal structures of

bacterial glycosylases (Fpg/Nei family of proteins) with the lesion in the active site, and found something she wasn't expecting. "The binding pocket had very few interactions with the lesion," she explained. "Our results suggest that glycosylases need to detect the lesion before binding."

Walking a tight rope

Wallace then looked towards single molecular studies to understand how these enzymes detected lesions on DNA. Her work showed short videos of glycosylase molecules moving back and forth on a piece of DNA stretched between two polylysine beads. This experiment allowed the observation of different diffusion patterns, or movements, of glycosylases on DNA, such as pause, slow, fast, and very fast. Wallace then wondered if the slow and fast diffusion behavior meant glycosylase was trying to find the lesion.

Upon further investigation, she found a residue on glyosylases, called a wedge residue that was involved in scanning the DNA to find the 8-oxoguanine lesions. These studies confirmed the hypothesis that glycosylases have a mechanism to scan the DNA looking for lesions.

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

The audience included several senior scientists, such as NIEHS lead researcher William Copeland, Ph.D., right, head of the Mitochondrial DNA Replication Group, and retired NTP geneticist Jack Bishop, Ph.D. (Photo courtesy of Steve McCaw)

Postdoctoral fellow Steven Roberts, Ph.D., was among the many trainees in the audience who turned out to hear a giant in the field of DNA repair. (Photo courtesy of Steve McCaw)

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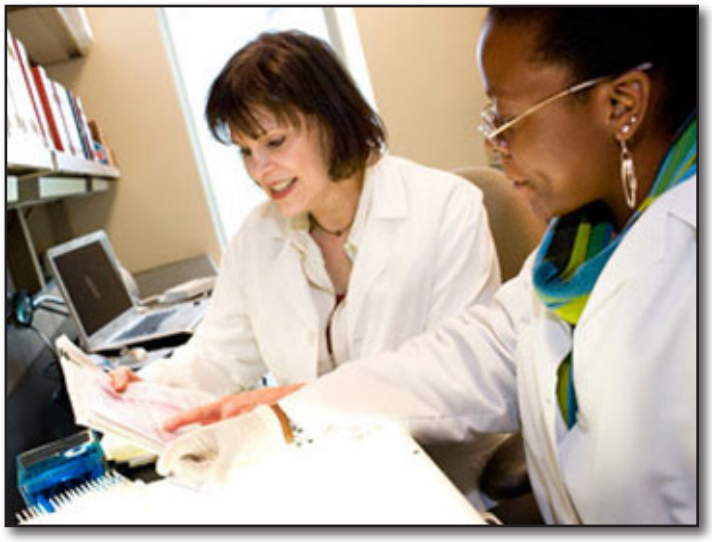
Webinar highlights advances in the study of autism

By Audrey Pinto

As investigators continue to search for clues that may help explain the causes of autism spectrum disorders (ASD), a group of complex developmental disorders, two NIEHS-funded scientists — Judy Van de Water, Ph.D., and Rebecca Schmidt, Ph.D. — are making significant strides in unraveling the mystery surrounding them.



Van de Water, left, thinks that an MAR test could become an important tool in family planning. (Photo courtesy of UCD)

In an Aug. 14 webinar, both scientists highlighted new findings from their studies conducted at the University of California, Davis (UCD) Center for Children's Environmental Health and MIND (Medical Investigation of Neurodevelopmental Disorders) Institute. Their research is clearly demonstrating that ASD goes beyond genetics.

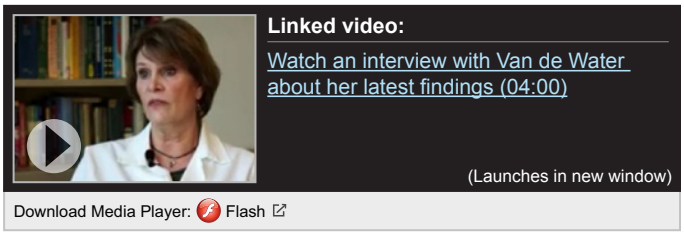
Van de Water and Schmidt are part of a nationwide network of children's centers supported by funding from NIEHS and the U.S. Environmental Protection Agency (EPA). Their presentations were part of the EPA/NIEHS Children's Centers 2013 Webinar Series.

Mother's autoantibodies may play a role in autism

Van de Water's research team has pinpointed evidence that specific antibodies target fetal brain proteins in the blood of some women whose children are diagnosed with autism. This finding may lead to a biomarker for early diagnosis and could also suggest targets for drug development. The researchers have named the autism related to these antibodies maternal autoantibody-related (MAR) autism. In July, their findings were published online in the journal Translational Psychiatry.

In earlier studies, Van de Water and her colleagues discovered that women with certain autoantibodies in their blood were at much greater risk of having a child with autism, and those children were much more likely to have severe symptoms of the disorder.

As Van de Water explained, "Antibodies interfere with normal protein function — the more antibodies, the more points of developmental interference, and the likelihood of autism increases." She went on to note that what triggers the autoantibodies leading to autism is unknown, but the work of her team indicates that these antibodies are a specific cause for a significant portion of autism cases. The next step is to develop an MAR diagnostic test that would show a near-certain risk of autism. This objective is now within reach.



New findings suggest that maternal iron deficiency may be linked to autism

Schmidt and her colleagues, who were the first to report that women who take the recommended daily dosage of folic acid, or vitamin B-9, during the first month of pregnancy had a reduced risk of having a child with ASD, continue to provide more clues toward building a better understanding of autism.

In ongoing work, her team was first to find evidence of an association between maternal iron deficiency and ASD. Schmidt explained, "Iron is crucial to early neurodevelopment, and early life deficiency impairs cognition, as well as motor, social, and language development."

"In the brain, iron contributes to neurotransmitter production, myelination, and immune function," Schmidt continued. Her recent research suggests that dysregulation of all three of these pathways is associated with ASD, and these findings confirm what other studies have consistently shown — a higher prevalence of iron deficiency is found in association with ASD.

In future studies, Schmidt and her team plan to look at other nutritional factors that could potentially play a role in the development of autism, to identify mechanisms and pathways, and develop nutrient and dietary strategies that could prevent, and possibly treat, ASDs.

Schmidt's research has focused on the association of nutrient and nutritional supplement levels in mothers, with development of autism in their children. (Photo courtesy of Rebecca Schmidt)

Citation: Braunschweig D, Krakowiak P, Duncanson P, Boyce R, Hansen RL, Ashwood P, Hertz-Picciotto I, Pessah IN, Van de Water J. 2013. Autism-specific maternal autoantibodies recognize critical proteins in developing brain. Transl Psychiatry 3(7):e277.

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

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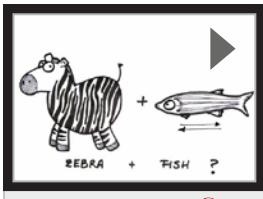
NTP talk explores zebrafish as a vertebrate model in toxicity screening

By Kristen Ryan

Arantza Muriana, Ph.D., gave a presentation Aug. 19 on the utility of zebrafish for toxicity testing, speaking by telephone to a capacity audience of NTP and NIEHS scientists with interests in the advancement of predictive toxicology. Her talk, "Zebrafish as a Tool for Screening and Prioritization of Chemicals for Toxicity Testing," was hosted jointly by the NTP Toxicology Branch (TB) and Biomolecular Screening Branch (BSB).

Muriana is director of Research and Development Management for Biobide S.L., an international contract research organization offering preclinical testing for early drug development. Biobide's unique specialty is providing the opportunity to rapidly assess numerous and complex aspects of drug-induced or chemical-induced toxicity in zebrafish.



Linked video:
Watch 'Drawn to Science: Zebrafish - a new model for drug discovery,' a charming video about this tiny fish that is having an enormous impact on toxicology and drug development (03:32)
(Launches in new window)

Download Media Player: Flash

"The NTP has been interested in identifying new strategies for screening and prioritizing compounds for *in vivo* testing, especially with the increasing nominations of classes of compounds such as flame retardants, PAHs, and phenolic benzotriazoles (PBZT)," said NTP contract toxicologist Mamta Behl, Ph.D., presentation host. "The zebrafish is a powerful tool to screen compounds, especially for early development, since it is a vertebrate, has a high genetic homology with humans, and the assays can be automated to provide relatively high-throughput along with high-content analysis."

An emerging model for toxicology and drug development

As Muriana explained, the adult and developing zebrafish are well established as model organisms for studies of vertebrate development, gene expression, and behavior, with over 12,000 research papers published within the last 10 years. In particular, zebrafish embryos have many applications, including the assessment of chemicals for their potential acute toxicity and teratogenicity, as well as organ-specific toxicities, including cardiotoxicity, hepatotoxicity, and neurotoxicity. At Biobide, she said, these assays have been developed to perform with a high degree of sensitivity and specificity, and can also be conducted under GLP (Good Laboratory Practice) testing regulations.

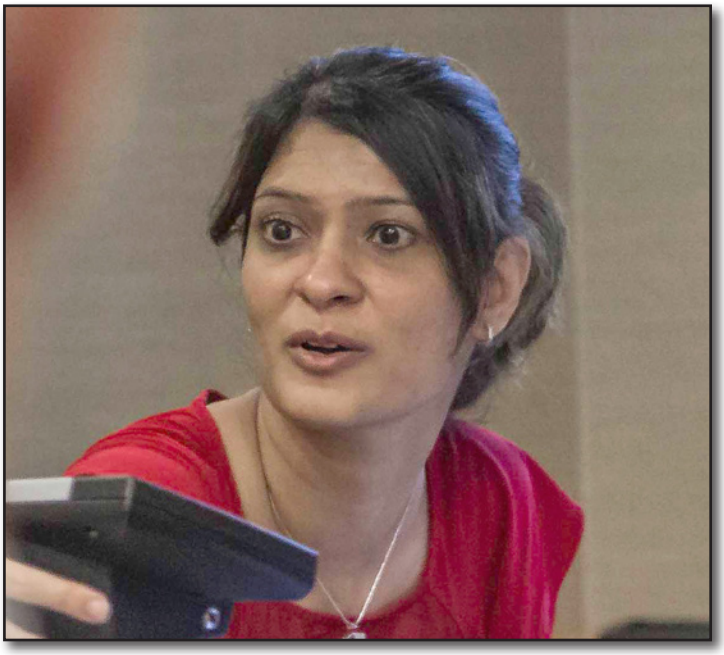
The zebrafish model is also adaptable to automated, high-throughput technologies, which are currently of interest to NTP (see text box).

During the seminar, Muriana highlighted the wide range of applications for toxicity testing in zebrafish, as well as Biobide's approach to refine and reduce the use of animals, while saving time and expense. At Biobide, a MultiTox Assay was developed to narrow down a large chemical set, by screening zebrafish through a particular sequence of assays, rather than performing one assay at a time.

Partnerships in zebrafish screening

NTP has several collaborations underway to examine the utility of zebrafish for screening and prioritizing chemicals, to ultimately serve as a model for *in vivo* hazard characterization:

- Robert Tanguay, Ph.D., at Oregon State University has tested over 3,000 compounds of interest to NTP, to complement the ongoing high-throughput screening efforts in the U.S. government's multiagency Tox21 research program. His research focuses on examining the effects of selected chemicals and chemical classes on zebrafish development and associated gene expression pathways (see related story).
- Christopher Weis, Ph.D., toxicology liaison in the NIEHS Office of the Director, and Stephanie Padilla, Ph.D., of the U.S. Environmental Protection Agency, are investigating the effects of flame retardants on zebrafish development, as well as behavior.



Behl introduced Muriana, whose talk was broadcast from Spain. Behl also moderated the question-and-answer session. (Photo courtesy of Michael Garske)

Can the model work for NTP?

While zebrafish seem to be ideal for drug development, individuals such as NTP contract pathologist Deepa Rao, Ph.D., questioned how well this strategy would work for environmental chemicals, since very little is known about their toxicity profiles at the onset of testing. Muriana pointed out that Biobide can customize assays. In response to a question on throughput from NTP molecular toxicologist Scott Auerbach, Ph.D., she estimated that nearly 100 compounds could be tested across three assays within three months' time.

A lively discussion led to several interesting questions from the audience, including one by TB head Paul Foster, Ph.D., about whether or not these assays, using embryos at day five, can accurately capture necessary windows of development for the urogenital system. Foster wondered whether longer-term assays can be conducted, to evaluate the effects of chronic exposures.

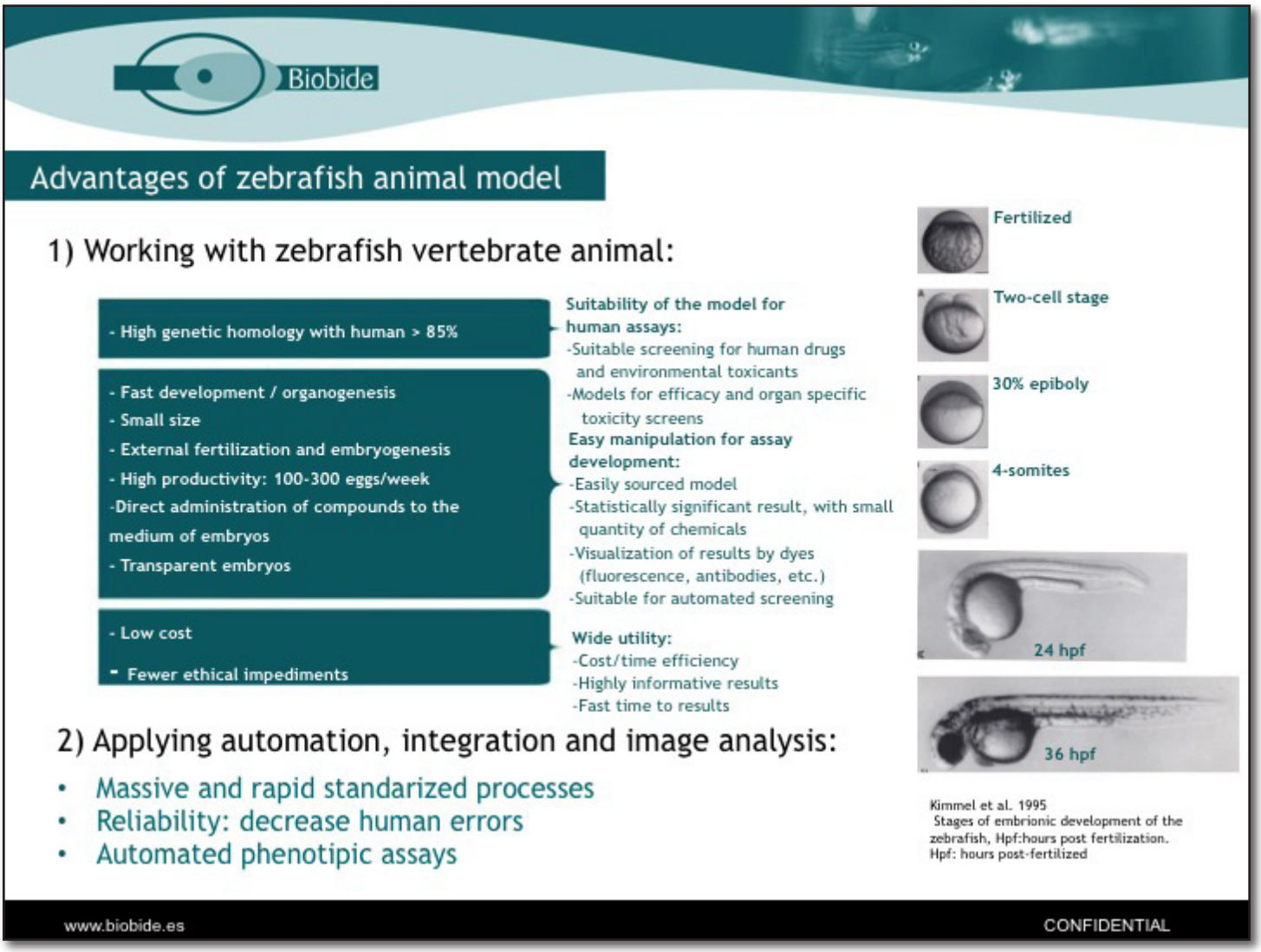
Overall, the seminar strengthened the growing appreciation for the value of zebrafish in toxicity testing, and brought insight to the program for future alternative and complimentary testing strategies within NTP.

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

Like some of her colleagues, Rao wanted assurance that the drug development screening model would work as well in toxicity screening. (Photo courtesy of Michael Garske)

BSB head Raymond Tice, Ph.D., described goals of the NTP predictive toxicology program. Seated beside him is Warren Casey, Ph.D., acting director of the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods, which has an explicit interest in refining and reducing the use of animals in testing. (Photo courtesy of Michael Garske)

Rachel Goldsmith, Ph.D., of the NTP WormTox Group, asked about characterization of COX2 genes in zebrafish, something Muriana said her company has yet to do. (Photo courtesy of Michael Garske)



Muriana used this slide to summarize the many advantages of the zebrafish model. (Image courtesy of Arantza Muriana)

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N.C. industrial livestock workers found to carry drug-resistant bacteria

By Nancy Lamontagne

Industrial livestock operations (ILOs) that use subtherapeutic doses of antibiotics could expose workers to drug-resistant bacteria, according to a new study co-funded by NIEHS. The researchers found methicillin-resistant *Staphylococcus aureus* (MRSA), with characteristics linked to livestock, in some people working at ILOs in North Carolina, but not in workers from antibiotic-free livestock facilities.

"Part of eastern North Carolina is the nation's densest area of hog production, and producers there commonly use subtherapeutic doses of antibiotics to promote livestock growth, a practice that is of great concern, due to its potential to promote antibiotic-resistant bacteria," said NIEHS grantee Steve Wing, Ph.D.

For the study, Wing's research team at the University of North Carolina at Chapel Hill Gillings School of Global Public Health collaborated with a team at Johns Hopkins Bloomberg School of Public Health led by Christopher Heaney, Ph.D.

Community involvement

The study presented some challenges for participants and the scientists. Industrial livestock workers in eastern North Carolina are predominantly low-income people of color, working in a region with a history of Jim Crow segregation and white supremacy, according to the researchers. There was also a potential for study participants to be concerned that corporate producers would retaliate against them if their participation in the study became known. To help facilitate the study, the Rural Empowerment Association for Community Help, a community-based organization that helps livestock workers and community members, was part of the research team.

"Community organizers helped plan the data collection, recruitment of industrial workers, and provision of information about the study results to industrial workers and other community members," said Wing. "Community organizers were essential for conducting the study, because they know the industry and community, and they promote workers' interests."

To evaluate the presence of MRSA, the investigators interviewed and obtained a nasal swab from 80 workers who were employed at ILOs, and 92 workers employed at farms that do not use antibiotics for growth promotion. Workers from ILOs showed a 42 percent prevalence of *Staphylococcus aureus* (*S. aureus*), and workers from antibiotic-free facilities exhibited a 38 percent prevalence. Three workers in each group carried MRSA.

Although the two groups exhibited similar *S. aureus* and MRSA prevalence, only workers from ILOs carried MRSA and multidrug-resistant *S. aureus* with characteristics associated with livestock. These characteristics included lack of the bacteriophage-encoded immune evasion cluster *scn* gene, which is present in most human *S. aureus*, and resistance to tetracycline, an antibiotic widely used as a livestock growth promoter. Additionally, *S. aureus*, belonging to a clonal complex associated with livestock in Europe (CC398), was considered an indicator of livestock association.

Funding

The research was supported in part by an NIEHS T32 training grant, along with funding from the North Carolina Translational and Clinical Sciences Institute, North Carolina Occupational Safety and Health Education and Research Center, the W.K. Kellogg Health Scholars Program – Community Track, a Gillings Innovation Laboratory award from the UNC Gillings School of Global Public Health, and other sources.

Wing said that community organizers were key for this study, which looked at the prevalence of antibiotic-resistant S. aureus in North Carolina livestock workers. (Photo courtesy of Steve Wing)

Health concerns

The study participants did not report any symptoms of infection. However, the presence of drug-resistant *S. aureus* is of public health importance, because if a person develops an antibiotic-resistant *S. aureus* infection, it would potentially be difficult to treat. The findings are also concerning, because strains of drug-resistant *S. aureus*, first detected among farm workers in Europe, showed up later in hospitals and communities there. However, Wing said that it is important to keep in mind that presence of *S. aureus* without infection is common in the general population.

The researchers are now examining the persistence of *S. aureus* in industrial livestock workers. The investigators recently completed data collection for a small repeated-measures study of workers employed in factory hog farms, to evaluate whether *S. aureus* presence is affected by time away from work.

Citation: Rinsky JL, Nadimpalli M, Wing S, Hall D, Baron D, Price LB, Larsen J, Stegger M, Stewart J, Heaney CD. 2013. Livestock-associated methicillin and multidrug resistant Staphylococcus aureus is present among industrial, not antibiotic-free livestock operation workers in North Carolina. PLoS One 8(7):e67641.

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

Many industrial livestock operations raise animals in close confinement and use antibiotics for growth promotion, providing an ideal environment for the exchange of new antibiotic-resistant bacteria between animals and humans. (Photo courtesy of the book "CAFO")

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Zebrafish developmental assays test the safety of new chemicals

By Sara Mishamandani

A group of molecules developed to break down pollutants in water is one step closer to commercial use, thanks to developmental tests led by Robert Tanguay, Ph.D., of the Oregon State University (OSU) Superfund Research Program. Tanguay's study, using developing zebrafish embryos, showed that the molecules designed to remove hazardous substances from water, called TAML activators, are not harmful themselves.

Tanguay assesses the health of adult zebrafish. (Photo courtesy of Robert Tanguay)

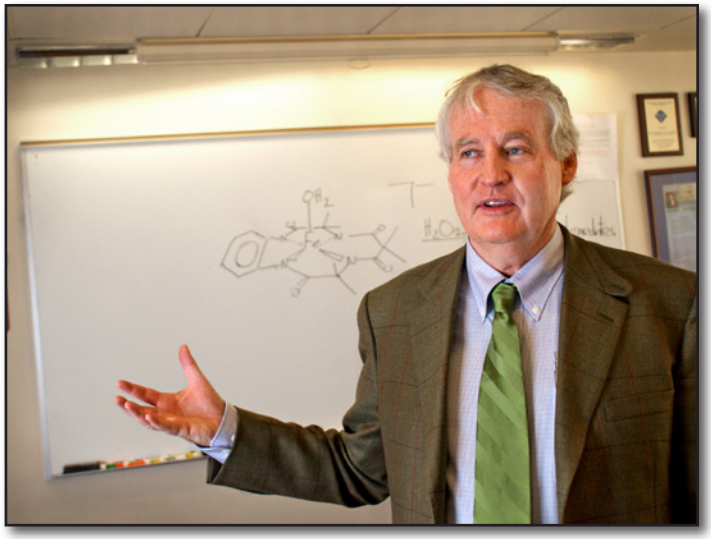
Green chemicals to clean up contaminated water

According to a press release from Carnegie Mellon University, TAML activators, created by chemist and study co-author Terrence Collins, Ph.D., provide an environmentally friendly method for breaking down toxic compounds that contaminate water, including endocrine disruptors.

Endocrine disruptors, which are found in almost 25 percent of streams, rivers, and lakes, can disrupt normal functions of the endocrine system and impair development, by mimicking or blocking the activities of hormones in wildlife. Several animal studies suggest that endocrine disruptors can also affect human health, and may be involved in cancers, learning disabilities, obesity, and immune and reproductive system disorders.

Previously, Collins and his collaborators showed that TAMLs, used with hydrogen peroxide, can easily and effectively remove steroid hormones, common endocrine disruptors, from water after just one treatment.

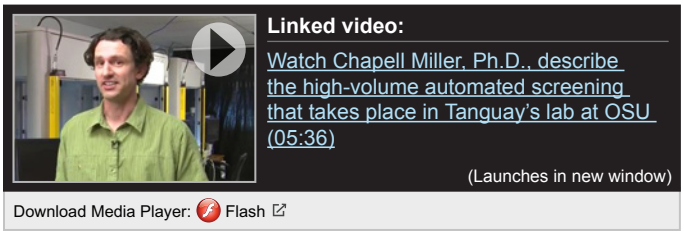
"Quite a few common commercial chemicals cause endocrine disruption," said Collins. "Before TAML activators are commercialized for treating municipal water, it is important to be sure that they aren't introducing, into the water, the very problem they were designed to reduce or eliminate."



Collins is a leading proponent of green chemistry who won a 2010 Heinz Award for his work to improve environmental health. (Photo courtesy of the Heinz Family Foundation)

Using zebrafish as a model system

Tanguay's group tested several TAML activators to determine whether they exhibit endocrine disrupting capability. Researchers exposed zebrafish embryos to seven different types of TAML activators. At concentrations typically used for decontaminating water, none of the TAML's impaired embryo development.



The zebrafish tests represent just one step in a series of tests that can be used to confirm that a chemical is free of endocrine disrupting activity. The test is part of a five-part testing system called the Tiered Protocol for Endocrine Disruption (TiPED), which was developed to determine potential endocrine disrupting activity in a chemical. The zebrafish tests are in tier four of the system, which ranges from computer-based approaches to tests in fish, animals, and human cells.

"In early development, as we develop from a single cell into a complex organism, the process by which a human does that is almost exactly the same as in zebrafish," said Tanguay. "So when we are asking if a compound could be hazardous to human development, we obviously can't do those studies in humans, but we can do them using zebrafish."

Tanguay's lab tests the impacts of chemicals on zebrafish, a small fish popular in home aquariums and even more useful for research. They reproduce in a matter of hours and, as they grow, changes are visible in their transparent embryos. (Photo courtesy of Robert Tanguay)

Moving forward

Collins and collaborators have already conducted, or are currently conducting, tests on TAMLs using assays in other TiPED tiers. In all cases, thus far, the tests demonstrated that TAML activators can be designed to treat water and not cause developmental disruption in aquatic organisms.

"These collaborative studies collectively provide a model that can be copied, time and time again, by chemists interested in producing chemicals known to be free of developmental disruption by the highest standards of contemporary science, as a way to advance the sustainability of our global civilization," Collins said.

Citation: Truong L, DeNardo MA, Kundu S, Collins TJ, Tanguay RL. 2013. Zebrafish assays as developmental toxicity indicators in the green design of TAML oxidation catalysts. Green Chem; doi:10.1039/C3GC40376A [Online 15 July 2013].

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

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Inhibitors of DNA topoisomerase and its repair enzymes in cancer treatment

By Deepa Singh

Fellows of Laboratory of Molecular Genetics (LMG) welcomed pharmacologist Yves Pommier, M.D., Ph.D., for a talk on cancer therapeutic research Aug. 12 at NIEHS. The event was hosted by Jordan St. Charles, Ph.D., a postdoctoral fellow in the DNA Replication Fidelity Group, headed by Thomas Kunkel, Ph.D.

Pommier received an NIH merit award for his contribution in elucidating the function of DNA topoisomerases as targets for anticancer drugs, as well as a Federal Technology Transfer Award for studies on DNA topoisomerase inhibitors. (Photo courtesy of Michael Garske)

Pommier described his work with DNA topoisomerases, a target of several anticancer drugs routinely used today. Most of the topoisomerase inhibitors approved by the U.S. Food and Drug Administration are utilized to treat colon, lung, and ovarian cancer, as well as pediatric tumors. These inhibitors target DNA or its activities, such as replication, recombination, and repair, to impede malignant cell proliferation.

Pommier is chief of the Laboratory of Molecular Pharmacology at the National Cancer Institute. In an effort to discover novel topoisomerase inhibitors and optimize their use in combination with other anticancer agents, Pommier's lab has been working with Mark Cushman, Ph.D., of Purdue University, to develop a new family of topoisomerase inhibitors now in phase I clinical trials at NIH.

DNA topoisomerase — a popular target for anticancer drugs

DNA topoisomerases, also known as the vertebrate DNA untwisting enzymes, are found in a variety of organisms and act to regulate DNA supercoiling. DNA topoisomerase 1 (Top1), which belongs to type IB and was the focus of Pommier's talk, is found in the nuclear genome and is not transported into the mitochondria, at least in mammals. However, research in Pommier's lab led to the discovery of a topoisomerase gene that is specific for mitochondrial DNA (Top1mt). As Pommier explained, "There is a division of labor in the vertebrate cell for the two genomes, nuclear and mitochondrial, each of them having its own Top1."

This enzyme cleaves the DNA by covalently attaching its tyrosine residue to the 3'-end of the DNA. This Top1 cleavage complex (Top1cc) can be trapped by ubiquitous DNA altercations. Pommier's group has demonstrated, using many different substrates, that Top1 can be trapped on DNA sites containing lesions, such as single mismatch, as well as an abasic site or an oxidized base present on the DNA.

NIEHS DNA Repair and Nucleic Acid Enzymology Group head Samuel Wilson, M.D., center, was one of several LMG and Laboratory of Structural Biology lead researchers on hand for Pommier's talk. (Photo courtesy of Michael Garske)

Developing the next generation of cancer therapies

Anticancer drugs, such as camptothecin (CPT) and several of its derivatives, also efficiently trap Top1, using a similar mechanism as seen for the DNA lesions. Using X-ray crystallography, Pommier's group has shown that, while interacting with Top1, CPT stacks itself between the DNA bases, thereby preventing the DNA re-ligation. Thus the trapped Top1cc generates cytotoxicity and anticancer activity.

This mechanism, known as interfacial inhibition, is unique and is different from the classical catalytic inhibition. Because CPT is chemically unstable, Pommier's lab has synthesized new compounds that are not activated chemically and can trap Top1 at different genomic sites.

Pommier's group is continuing efforts to characterize human cancer cell lines, to determine the factors and genes that govern drug susceptibility. Ongoing research is looking at novel ways to capitalize on the synergistic potential of multiple agents and design selectively targeted cancer treatments that also reduce the harmful side effects of currently used therapies (see text box).

Targeting Top1 repair enzymes

In his search for better inhibitors, or the best combination of different inhibitors, Pommier focused on enzymatic pathways that closely work with Top1. These are the repair pathways that clean up the Top1-DNA adduct, before the DNA is re-ligated. One such enzyme is tyrosyl-DNA phosphodiesterase (TDP1), which hydrolyses the bond between Top1 and DNA. Pommier's team and other groups have demonstrated that TDP1-deficient human cells are hypersensitive to CPT. In his recent work, Pommier has shown that TDP1 can also remove chain-terminating nucleoside analogs (CTNAs) that are widely used as antiviral and anticancer drugs. These CTNAs block the 3'-end of a single-strand DNA, forming a DNA lesion. "This work carries important implications in anticancer therapy, as it lets us understand how cells repair the DNA damage induced by CTNAs," he said of the findings.

Similarly, another enzyme, poly (ADP-ribose) polymerase (PARP) 1, binds and reseals the single-strand breaks (SSBs) in the DNA during the repair of Top1cc. Thus, PARP1 and TDP1 have epistatic roles in the repair of Top1cc. It is also known that inhibitors of PARP have an antitumor effect, as they block the repair of SSBs. Pommier's lab has shown that these inhibitors act like a poison and trap PARP at damaged DNA, similar to CPT. This finding suggests that PARP inhibitors could also be used effectively in the treatment of cancer.

NIEHS Chromosome Stability Group cancer researchers, from right, staff scientist Daniel Menendez, Ph.D., postdoctoral fellow Steven Roberts, Ph.D., and senior associate scientist Dmitry Gordenin, Ph.D., also attended the talk. (Photo courtesy of Michael Garske)

As host, St. Charles, center, moderated the questions that followed Pommier's talk. (Photo courtesy of Michael Garske)

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

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This month in EHP

This month, Environmental Health Perspectives (EHP) focuses on advances in combating aflatoxins in the food supply, and explores the gut microbiome in health and disease. EHP editors also extend their congratulations to authors of the International Society for Environmental Epidemiology (ISEE) 2012 best paper of the year, which was published in the December 2012 issue of the journal (see text box).

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Breaking the Mold: New Strategies for Fighting Aflatoxins

Aflatoxin B1, the most potent naturally occurring liver carcinogen ever identified, is produced by *Aspergillus* fungi that infect crops during periods of drought stress and intense heat. Although found around the world, aflatoxins pose a human health threat primarily in developing countries. Researchers and development groups are investigating a variety of new methods to keep these agents out of food supplies.

The Environment Within: Exploring the Role of the Gut Microbiome in Health and Disease

A growing body of research suggests that part of what determines how the human body responds to external stimuli may be not only our own genes, but also the genes of the trillions of microorganisms that reside on and in the human body. New studies are shedding light on the ways that microorganisms in the intestinal tract influence biological functions beyond the gut and play a role in diseases throughout the body.

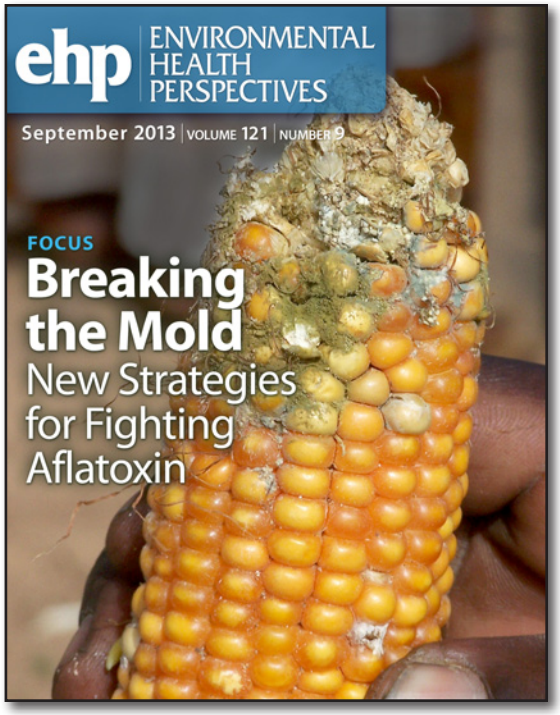
Featured research and related news articles this month include:

- **Retinal Microvascular Responses to Short-term Changes in Particulate Air Pollution in Healthy Adults** — Particulate Matter and Cardiovascular Disease: Researchers Turn an Eye Toward Microvascular Changes

- **Improved Air Quality and Attenuated Lung Function Decline: Modification by Obesity in the SAPALDIA Cohort** — Respiratory Disparity? Obese People May Not Benefit from Improved Air Quality

- **Perinatally Administered Bisphenol A Acts as a Mammary Gland Carcinogen in Rats** — BPA as a Mammary Carcinogen: Early Findings Reported in Rats

- **Instruments for Assessing Risk of Bias and Other Methodological Criteria of Published Animal Studies: A Systematic Review** — Bias Detection: Study Identifies Instruments for Evaluating Animal Studies



ISEE Best Environmental Epidemiology Paper Published in 2012

The International Society for Environmental Epidemiology has selected "Birth Weight, Head Circumference, and Prenatal Exposure to Acrylamide From Maternal Diet: The European Prospective Mother-Child Study (NewGeneris)" for its 2012 Best Environmental Epidemiology Paper Award. The award was presented in August at the 2013 ISEE Annual Conference.

EHP congratulates authors Marie Pedersen, Hans von Stedingk, Maria Botsivali, Silvia Agramunt, Jan Alexander, Gunnar Brunborg, Leda Chatzi, Sarah Fleming, Eleni Fthenou, Berit Granum, Kristine B. Gutzkow, Laura J. Hardie, Lisbeth E. Knudsen, Soterios A. Kyrtopoulos, Michelle A. Mendez, Domenico F. Merlo, Jeanette K. Nielsen, Per Rydberg, Dan Segerbäck, Jordi Sunyer, John Wright, Margareta Törnqvist, Jos C. Kleinjans, Manolis Kogevinas, and the NewGeneris Consortium.

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Extramural papers of the month

By Nancy Lamontagne

- Cigarette smoke affects genes associated with heart and lung health
- Graphene sheets pierce and enter cells
- Global cost of childhood lead exposure
- Understanding the cytotoxicity of hexavalent chromium

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

Cigarette smoke affects genes associated with heart and lung health

An NIEHS-funded mouse study provides evidence that sidestream cigarette smoke, the secondhand smoke from burning tobacco, affects the activity of hundreds of genes that protect the heart and lungs. Obese mice on a high-fat diet showed the strongest response after inhaling sidestream smoke.

Smoking and obesity are risk factors for cardiovascular disease, but the molecular mechanisms behind the increased risks are not well understood. The researchers used mouse models to study early signaling events that occur in the heart and lungs after cigarette smoke exposure. They also looked at the role of obesity in this response. The investigators exposed normal weight and obese mice fed a high-fat diet to the two components of secondhand smoke — exhaled mainstream smoke and the side stream smoke emitted from the burning tip, the latter of which makes up 85 percent of secondhand smoke.

Using whole genome microarray analysis, the investigators found that mice exposed to mainstream smoke showed cellular and molecular inflammatory responses in the lung. The normal weight animals had 1,466 differentially expressed pulmonary genes and 463 differentially expressed cardiac genes. Exposures to sidestream smoke brought a weak pulmonary response (328 genes) but a strong cardiac response (1,590 genes). In general, the most sensitive smoke-induced cardiac transcriptional changes observed in the normal weight mice were not observed in the smoke-exposed obese mice. The smoke exposure also suppressed multiple proteome maintenance genes induced in the hearts of obese mice. Overall, the results showed that the heart is sensitive to sidestream smoke and that adaptive responses in healthy mice were absent in obese mice.

Citation: Tilton SC, Karin NJ, Webb-Robertson BJ, Waters KM, Mikheev V, Lee KM, Corley RA, Pounds JG, Bigelow DJ. 2013. Impaired transcriptional response of the murine heart to cigarette smoke in the setting of high fat diet and obesity. Chem Res Toxicol 26 (7):1034–1042.

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Graphene sheets pierce and enter cells

NIEHS grantees report that graphene materials with micrometer-scale dimensions, known as graphene microsheets, can enter cells when their sharp protrusions pierce the cell membrane. Understanding how these graphene sheets interact with cells can help scientists develop materials that are not harmful to the body.

The researchers' initial simulations suggested that a microsheet would rarely pierce a cell, because the energy barrier required for a sheet to cut the membrane was too high. However, when these simulations took into account the rough edges commonly found on the edges of graphene sheets, the sheets more easily pierced the membrane.

Confocal fluorescence and electron microscopy confirmed that graphene's rough edges and corners could pierce primary human keratinocytes, human lung epithelial cells, and murine macrophages. The imaging also showed that cells could completely internalize graphene sheets with lateral dimensions of 0.5 to 10 micrometers. More research is needed to understand how the microsheets affect cells, but the researchers say that microsheets might disrupt cytoskeleton and cell motility, and cause problems with epithelial barriers.

Citation: Li Y, Yuan H, von dem Bussche A, Creighton M, Hurt RH, Kane AB, Gao H. 2013. Graphene microsheets enter cells through spontaneous membrane penetration at edge asperities and corner sites. Proc Natl Acad Sci U S A 110(30):12295-12300.

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Global cost of childhood lead exposure

According to research supported by NIEHS, low-income and middle-income countries experience the largest burden of lead exposure, with cost measured in what are known as international dollars. An international dollar is a hypothetical currency used to compare costs from various countries. It has the same purchasing power as a dollar would in the U.S.

The investigators estimate that childhood lead exposure in low-income and middle-income countries is associated with lost lifetime economic productivity of $977 billion international dollars annually, or 1.2 percent of the world's gross domestic product. For comparison, lead-associated loss in lifetime economic productivity is estimated to be $50.9 billion international dollars in the U.S. and $55 billion international dollars in Europe.

The researchers calculated lead-associated loss, by developing a regression model to estimate average blood lead levels and estimating the lead-attributable economic costs with an environmentally attributable fraction model. They examined only the neurodevelopmental effects of lead, which were assessed using IQ points. The investigators estimate that the total lead-associated economic loss ranges from $728.6 to $1,162.5 billion international dollars, including $134.7 billion in Africa, $142.3 billion in Latin America and the Caribbean, and $699.9 billion in Asia.

Citation: Attina TM, Trasande L. 2013. Economic costs of childhood lead exposure in low- and middle-income countries. Environ Health Perspect; dx.doi.org/10.1289/ehp.1206424 [Online 25 June 2013].

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Understanding the cytotoxicity of hexavalent chromium

In a study funded in part by the NIEHS, researchers report that hexavalent chromium, or CR(VI), cytotoxicity may partially result from its up-regulation of cholesterol biosynthesis. Cr(VI) is generated during industry processes and is carcinogenic. A better understanding of the mechanisms for the cytotoxicity of this heavy metal could be used to develop therapies that decrease health effects after exposure.

The researchers used stable isotope labeling by amino acids in cell culture and liquid chromatography coupled with tandem mass spectrometry to study the cellular mechanisms affected by Cr(VI). This quantitative proteomic technique revealed 4,607 unique proteins involved in Cr(VI) perturbation of cells. Of these, 270 proteins were significantly up-regulated and 127 down-regulated.

The researchers found that Cr(VI) affected cholesterol biosynthesis, G-protein signaling, inflammatory response, and selenoprotein pathways. Cells treated with Cr(VI) had much higher expression of a large number of enzymes involved in cholesterol biosynthesis, and multiple cell lines showed increases in cellular cholesterol levels. In addition, the cholesterol-lowering drug, lovastatin, reduced growth inhibition of cultured human cells brought on by Cr(VI).

Citation: Guo L, Xiao Y, Wang Y. 2013. Hexavalent chromium-induced alteration of proteomic landscape in human skin fibroblast cells. J Proteome Res 12(7):3511-3518.

(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 Jacqueline de Marchena, Monica Frazier, Melissa Kerr, and Bailey Schug

- APOBEC cytidine deaminases generate many mutations in human cancers
- Observing a DNA polymerase using time-resolved crystallography
- How specific stressors alter p53 binding and transactivation
- Early mouse development influences norepinephrine neuron diversity

APOBEC cytidine deaminases generate many mutations in human cancers

NIEHS researchers and colleagues at the Broad Institute of MIT and Harvard in Cambridge, Mass., report that a set of proteins, known to protect against retroviruses and retrotransposons, can cause mutations that are widespread in human cancers.

These mutations, which have a characteristic mutation signature, are produced by apolipoprotein B mRNA-editing enzyme, catalytic polypeptide-like (APOBEC) cytidine deaminases. Scientists from the team developed an analysis to detect and statistically evaluate the prevalence of APOBEC mutations in 2,680 tumor samples, collected from 14 types of cancer. Using this strategy, they discovered that APOBEC enzymes produce the majority of mutations in some bladder, cervical, breast, head and neck, and lung tumors.

These researchers also found APOBEC signature mutations specifically in genes that have been implicated in cancer development and progression, highlighting a potential link between APOBEC enzymes and carcinogenesis. Furthermore, the tumor samples demonstrated a direct correlation between the levels of APOBEC3B and APOBEC3A mRNA transcript and the prevalence of APOBEC-type mutations. However, it is likely that

APOBEC expression acts in concert with other factors to drive APOBEC mutagenesis. The authors suggest that APOBEC mutations may also be facilitated by any factor that increases the prevalence of single-stranded DNA, including DNA damaging agents. **(JDM)**

Citation: Roberts SA, Lawrence MS, Klimczak LJ, Grimm SA, Fargo D, Stojanov P, Kiezun A, Kryukov GV, Carter SL, Saksena G, Harris S, Shah RR, Resnick MA, Getz G, Gordenin DA. 2013. An APOBEC cytidine deaminase mutagenesis pattern is widespread in human cancers. Nat Genet; doi:10.1038/ng.2702 [Online 14 July 2013]. Story

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Observing a DNA polymerase using time-resolved crystallography

NIEHS scientists utilized a technique called time-resolved crystallography to examine how a model human DNA polymerase beta (pol beta) chooses a nucleotide during DNA synthesis. The researchers employed natural substrates and followed product formation in real time with 15 different crystal structures. They were able to observe molecular adjustments at the active sites that hasten correct nucleotide insertion and deter incorrect insertion.

The X-ray crystallography technique they used confirmed features of the computational results the researchers had generated earlier, but also revealed new information. They found that pol beta changes its shape, depending on whether it incorporates a complementary base pair or correct nucleotide. This action permitted researchers to isolate and characterize intermediate structures during nucleotide insertion, helping assess and identify fidelity checkpoints at a structural level.

The study also found that pol beta forms a third metal binding site during correct, but not incorrect, nucleotide insertion, and pyrophosphate more easily dissociates after incorrect nucleotide insertion. Prior to this evidence, researchers believed that only two metal ion binding sites were used by all polymerases in their mechanism of action and pyrophosphate was released instantly. The researchers hope this information will lead to a better understanding of the potential causes of disease. **(BS)**

Citation: Freudenthal BD, Beard WA, Shock DD, Wilson SH. 2013. Observing a DNA polymerase choose right from wrong. Cell 154(1):157-168. Story

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How specific stressors alter p53 binding and transactivation

Scientists from NIEHS determined that a variety of stresses can change how the transcription factor p53, a well-known tumor suppressor, binds to DNA across the genome in human cancer cells. The team also discovered 149 new genes targeted by the p53 transcription factor, including several that are important in tumor suppression. The findings may help researchers develop better cancer treatment therapies.

In this study, the authors investigated the differences in p53 binding patterns and transcriptional responses, after exposing osteosarcoma cells to the DNA damaging agent Doxorubicin and the p53 stabilizer Nutlin-3. Interestingly, they found their DMSO vehicle treatment also induced a large degree of DNA binding by p53,

but this binding was not associated with the transactivation of genes, as was observed for Doxorubicin and Nutlin. Both treatments resulted in stress-specific transcriptional responses.

In addition to discovering that just half the consensus-binding motif was sufficient in vivo for binding, they found many new putative p53 target genes that are associated with a milieu of critical processes, such as DNA repair and immune responses. These findings will be extremely useful to the future identification of novel therapeutic targets in cancer treatment. **(MF)**

Citation: Menendez D, Nguyen TA, Freudenberg JM, Mathew VJ, Anderson CW, Jothi R, Resnick MA. 2013. Diverse stresses dramatically alter genome-wide p53 binding and transactivation landscape in human cancer cells. Nucleic Acids Res; doi:10.1093/nar/gkt504 [Online 17 June 2013].

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Early mouse development influences norepinephrine neuron diversity

Applying a technique known as intersectional genetic fate mapping to the developing mouse brain, NIEHS researchers characterized neurons that produce and release norepinephrine (NE), a hormone and neurotransmitter, and, for the first time, developed a map of their communication pathways. Since NE neurons are involved in several physiological processes, such as food intake and sleep, and are lost in Parkinson's and Alzheimer's diseases, understanding NE neurons will lead to improvements in human health.

The research team labeled NE neurons in the fetal mouse and followed their maturation. The scientists found that NE neurons, derived from a specific rhombomere, or segment in the developing hindbrain, shared common features in the adult brain. Team members used this information to create a novel system for grouping NE neurons.

The group also determined that these various subgroups of NE neurons were talking to many different parts of the adult mouse brain, including the amygdala, hippocampus, hypothalamus, and many more. Prior to this study, neuroscientists believed only one group of NE neurons communicated with the cerebral cortex. The results will provide valuable groundwork for the study of particular NE neurons and the impact diseases or environmental exposures have on them. **(MK)**

Citation: Robertson SD, Plummer NW, de Marchena J, Jensen P. 2013. Developmental origins of central norepinephrine neuron diversity. Nat Neurosci 16(8):1016-1023. Story

(Jacqueline de Marchena, Ph.D., is an Intramural Research Training Award (IRTA) fellow in the Laboratory of Neurobiology. Monica Frazier, Ph.D., is an IRTA fellow in the NIEHS Laboratory of Molecular Genetics. Melissa Kerr studies chemistry at North Carolina Central University and is an intern in the NIEHS Office of Communications and Public Liaison. Bailey Schug studies health promotion and nutrition at Appalachian State University and is an intern in the NIEHS Office of Communications and Public Liaison.)

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Inside the Institute

Feds Feed Families sets new record with 2013 food drive

By Allison Eason

NIEHS employees concluded the 2013 Feds Feed Families campaign with its third and final collection Aug. 28, for a total of 3,612 pounds of donated non-perishable food and personal hygiene items. The drive exceeded its goal of 3,500 pounds and topped the previous record set last year.

The coordinators gathered with a sample of the fruits of their labors — food and hygiene items for people in the community needing a hand-up in a difficult economy. Shown above, from left, are Withers, Brace, and Jirles. (Photo courtesy of Steve McCaw)

This marks the fourth year of NIEHS support for the Durham Rescue Mission (DRM) and the Food Bank of Central and Eastern North Carolina (FBCENC).

Coordinators for the 2013 campaign were Office of Management representative Monya Brace, President of the American Federation of Government Employees Local 2923 Bill Jirles, and Blacks In Government Research Triangle Park Chapter representative Sheila Withers. Because of their efforts, NIEHS maintains its ranking as one of the most generous organizations in the area and a top performer nationwide.

DURHAM RESCUE MISSION
Mending Shattered Lives Since 1974

Part of a nationwide effort

Since 2009, federal workers have collected and donated 15.2 million pounds of food and other non-perishable items, 7.2 million pounds in 2012 alone, to support families across the U.S. This year marks the fifth Feds Feed Families food drive.

Feds Feed Families accepts food items such as canned seafood, meats, meals, fruits and vegetables, as well as cereal, peanut butter, juice, rice, pasta, and dried beans, in non-glass containers. Infant diapers, wipes, and hygiene products, are also collected.

At NIEHS, items were donated at the main entrances of the Rall and Keystone buildings, 102 building, and the Clinical Research Unit, as well at other locations in the buildings.

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

FOOD BANK OF CENTRAL & EASTERN NORTH CAROLINA

The campaign's banner was hard to miss, as it stretched along the sidewalk of the NIEHS main building. (Photo courtesy of Steve McCaw)

Brace smiles as her van began to fill with food and hygiene items from the final collection at the NIEHS Keystone Building. (Photo courtesy of Steve McCaw)

As this photo from the June collection shows, the drive collected a wide range of items from generous employees and contractors. (Photo courtesy of Steve McCaw)

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Friends and colleagues remember Walter Olds

By Richard Sloane

Friends and colleagues were saddened by news of the death Aug. 22 of NIH retiree Walter Olds at age 87 in Cary, N.C., following a period of illness with the rare degenerative muscle disease, myopathy (see obituary and slide show of family photos).

Olds was born Feb. 1, 1926 in Akron, Ohio. After serving in the U.S. Navy, he became an architect. In 1981, he joined NIEHS as an engineer in NIH Office of Research Facilities at NIEHS, formerly the Facilities Engineering Branch. He retired in 1996, saying he needed more time to get on with his life.

After retirement, Olds served as a gem cutter with the jewelry firm Charles and Colvard. He enjoyed photography and traveling. His photographs of the American Southwest and extensive images of grist mills in the Southeast were a delight to all regional photographers. Olds did his own darkroom work and was one of the pioneering forces behind the former, very successful NIEHS Camera Club, serving as its treasurer for more than a decade.

Olds got together regularly with his friends from NIEHS and clearly enjoyed his retirement years. (Photo courtesy of Richard Sloane)

Among his many accomplishments and successes, the most notable may have been the many closely held relationships he greatly valued, some measured not by years but decades. Many of these were with his photography friends at NIEHS and other regional camera clubs. His humor, smile, and zest for life, pizza, and ice cream were contagious. All of his friends, new and old, celebrate a life well-lived, and raise a glass in his memory in thanks for great times and wonderful memories.

A memorial service was held Aug. 28 at Brown-Wynne Funeral Home in Cary, N.C. Olds is survived by partner Marlene Barnard, two brothers, two sisters, four children, and two grandchildren.

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

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National Institute of Environmental Health Sciences

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