National Institute of Environmental Health Sciences

Environmental Factor

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April 2013

NIEHS Spotlight

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In EHP editorial, Birnbaum calls new report mandatory reading

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Strengthening research and community partnerships in the Gulf

More than 80 researchers and community partners gathered for the NIEHS Deepwater Horizon Research Consortia's stakeholder meeting in New Orleans Feb. 22-23.

Balbus discusses health impacts of climate change at Senate briefing Video

The session brought together four climate change experts, including NIEHS Senior Advisor for Public Health John Balbus, M.D., Feb. 13 in Washington, D.C.

Science Notebook

Falk lecture highlights the importance of microbes in chronic disease

Infectious disease epidemiologist Julie Parsonnet, M.D., discussed her work as the featured speaker for the 2013 Hans L. Falk Memorial Lecture March 19.

Nano consortium hits stride in middle age

Now in its third year, the consortium's eight centers gathered once more at NIEHS Feb. 25-26 for an annual review of its progress toward its ambitious goals.

Friend promotes a revolution in biomedical research Video

Researchers at NIEHS and guests from nearby institutions had an opportunity March 1 to hear from scientist and visionary Stephen Friend, M.D., Ph.D.

First two substances peer reviewed for listing in new Report on Carcinogens

A panel of experts concurred with the preliminary decision by NTP to list 1-bromopropane and cumene as reasonably anticipated human carcinogens.

Study uncovers details of allergic response in asthma patients

According NIEHS scientists, an enzyme normally produced in the body to help fight inflammation, also suppresses allergic responses in asthma patients.

NIEHS Spotlight

Balancing economic development with air pollution curbs Video

A new NIEHS-funded study, published in Environmental Justice, chronicles development and progress of the Trade, Health, Environment Impact Project.

Panel highlights climate change science that can improve global health

NIEHS convened a plenary panel on infectious and non-communicable disease March 16 at a conference of the Consortium of Universities for Global Health.

Outreach workshop keeps teachers engaged Video

The NIEHS Rodbell Auditorium was abuzz with activity and laughter March 11 as 21 science teachers and educators joined in the Rx for Science Literacy workshop.

Family-friendly pilot project offers options for IRTA trainees

About half of the trainees working at NIEHS in established research programs could potentially qualify for an NIH pilot program known as Keep the Thread.

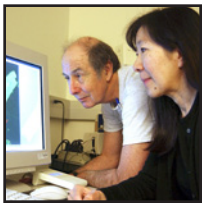
Smaller presence at SOT, but big enthusiasm for science

Although the NIEHS and NTP presence at this year's Society of Toxicology meeting was much smaller than usual, enthusiasm for science was still in abundance.

Former NIEHS research fellow enters medical school Video

Against incredible odds, former NIEHS research fellow Quiana Childress worked her way through college and is now about to enter Ross University School of Medicine.

Science Notebook



Potential new therapy for stopping cardiac fibrosis Video

A unique therapy for preventing or reducing harmful cardiac scar tissue may result from a new finding by NIEHS-supported researchers at the UC Davis.

Brown SRP scientists partner with ATSDR to discuss nano design

Brown University Superfund Research Program grantees spent Feb. 27 with colleagues at the Agency for Toxic Substances and Disease Registry in Atlanta.

UNC studies link viral infection response to smoking and nutrition

The effects appear to result from oxidant-driven gene expression changes that directly inhibit antiviral pathways in respiratory epithelium infected with flu virus.

Researchers offer recommendations for BPA study design

A new study finds that low-dose BPA studies do not have consistent results and argues that some of the discrepancies are likely due to basic rodent care issues.

NTP hosts review of endocrine disruptor screening

To help advance the Endocrine Disruptor Screening Program NTP and NIEHS hosted a Society of Toxicologic Pathology meeting March 21 on pathology endpoints.

Moving toward a new framework for chemical risk assessment

Grantee Russell Thomas, Ph.D., proposed a practical, data-driven framework that can provide a near-term solution during a presentation March 15 at NIEHS.

NIEHS Spotlight

Career fair to focus on the dynamic nature of biomedical careers

The 16th annual NIEHS career fair will be held April 26 at the U.S. Environmental Protection Agency Research Triangle Park, N.C., campus.

Calendar of Upcoming Events

- **April 5**, in Rodbell C, 11:00 a.m.-12:00 p.m. — Epidemiology Branch hosted presentation on "GWAS [Genome-Wide Association Studies] of Lung Cancer in Chinese: Current Findings and Future Strategies" by Hongbing Shen, M.D., Ph.D.
- **April 9**, in Rodbell Auditorium, 11:00 a.m.-12:00 p.m. — Distinguished Lecture Series, featuring Michael Cahalan, Ph.D., discussing "Cracking CRAC — The Calcium Release-Activated Calcium Channel of the Immune System"
- **April 11-12**, in Rodbell Auditorium, 8:30 a.m.-4:30 p.m. — "NIEHS Symposium on Unlocking the Promise of Stem Cells"
- **April 12**, in Rall D-450, 11:00 a.m.-12:00 p.m. — Epidemiology Branch hosted presentation on "Active Smoking and Breast Cancer Risk: An Update from the American Cancer Society's Cancer Prevention Study II Cohort and Meta-Analysis," by Mia Gaudet, Ph.D.
- **April 12 (offsite event)**, in the Levine Science Research Center, Room A247, at Duke University, 12:00-1:30 p.m. — Integrated Toxicology and Environmental Health Program Seminar Series with Ivan Rusyn, M.D., Ph.D., presenting "Bridging Computational Modeling and Wet-Bench Toxicology: Interdisciplinary Approach to Move the Field Forward"
- **April 17 (offsite event)**, in the Levine Science Research Center, Room A247, at Duke University, 12:00-1:30 p.m. — Integrated Toxicology and Environmental Health Program Seminar Series with Peter Thomas, Ph.D., topic TBA
- **April 19**, in Rodbell A, 11:00 a.m.-12:00 p.m. — Laboratory of Reproductive and Developmental Toxicology Seminar Series presentation on "ERalpha [Estrogen Receptor alpha] and Metabolic Disease," by Andrea Hevener, Ph.D.
- **April 26 (offsite event)**, at the U.S. Environmental Protection Agency in Research Triangle Park, N.C., 8:30 a.m.-5:00 p.m. — 16th Annual NIEHS Biomedical Career Fair
- **April 30**, in Rodbell Auditorium, 11:00 a.m.-12:00 p.m. — Distinguished Lecture Series, featuring Katsuhiko Mikoshiba, M.D., Ph.D., exploring "Role of IP3 [Inositol 1,4,5-trisphosphate] Receptor Signaling in Development, Cell Function, and Diseases"
- View More Events: NIEHS Public Calendar

Science Notebook

This month in EHP

This month's feature stories in Environmental Health Perspectives explore questions surrounding human risk for Lyme disease and the safety of food additives.

Distinguished Lecture Series talks to explore calcium signaling

Lead researcher James Putney, Ph.D., will host talks in April by two leaders in the field of calcium signaling, Mike Cahalan Ph.D., and Katsuhiko Mikoshiba, M.D., Ph.D.

Extramural Research

Extramural papers of the month

- Contaminated diet contributes to phthalate and bispenol A exposure
- PBDEs may increase risk for Parkinson's disease
- Father's obesity could have epigenetic effects
- SOD1 can repress respiration

Intramural Research

Intramural papers of the month

- Structurally similar endocrine-disrupting chemicals use same mechanism to activate estrogen receptors
- Mac-1 is a novel surface receptor of inflammatory response
- Consequences of ribonucleotide removal by topoisomerase 1
- Early-life exposures linked to early menarche in Sister Study

NIEHS Spotlight

Birnbaum speaks at White House summit

By Eddy Ball

NIEHS and NTP Director Linda Birnbaum, Ph.D., joined other environmental leaders March 20 for the 2nd Annual Women and the Environment Summit at the White House. The agenda featured talks by Birnbaum, senior scientific administrators from the U.S. Environmental Protection Agency (EPA), White House officials, and representatives of several non-profit advocacy groups, including NIEHS grantee Elizabeth Yeampierre, J.D., executive director of the United Puerto Rican Organization of Sunset Park and a member of the NIEHS Council.

"Environmental health matters because millions of lives can be improved by simply better understanding how the environment effects out health," Birnbaum told attendees. (Photo courtesy of Steve McCaw)

More than 100 women leaders in the environmental field, or related fields such as public health, engaged in three panels and four breakout sessions. The summit featured opening remarks by Gina McCarthy, the top air pollution regulator at EPA and President Obama's nominee to succeed Lisa Jackson as administrator, and Allison Whipple Rockefeller, founding chair of the Rachel Carson Awards Council. The Summit included briefings from White House Officials and three panel discussions with diverse business and community leaders from across the country, followed by breakout sessions.

The event, which was one of many celebrating Women's History Month nationwide, underscored the continued need for women to take an active role in protecting natural resources.

Focusing on environmental public health

Through her participation on the first panel of the day and in a breakout session on Healthy and Sustainable Communities, Birnbaum focused on the public health concerns that drive NIEHS research. She noted NIEHS initiatives in the areas of breast cancer, where the Institute invested more than $31 million in 2012 alone; noncommunicable diseases, most of which are linked to environmental factors; and children's health and development, which are disproportionately affected during windows of susceptibility by the exposure to chemicals inadequately regulated by the Toxic Substances Control Act.

A community organizer concerned with health of minority residents of Brooklyn, Yeampierre helped raise awareness of environmental justice issues with her participation on panel two. She is shown above during her presentation at NIEHS (see story) in October 2012. (Photo courtesy of Steve McCaw)

Turning to the burning issue of health care costs, Birnbaum offered an example of the cobenefits to be achieved through interventions to reduce harmful

environmental exposures. “In addition to just being the right thing to do — being good custodians of mother earth — preventing disease through improving the environment and reducing adverse exposures is one of the best ways to achieve health care cost reduction.”

Even though she wasn’t a part of the Environmental STEM (science, technology, engineering, and mathematics) and Careers breakout session, she spoke with pride about NIEHS efforts to support women’s scientific careers.

“The institute has a very strong history of promoting women in STEM careers, from kindergarten students through postdoctoral fellows,” she told the audience. “We are proud of the high-quality on-site day care facility, the flexible work schedules, telework options, and family friendly leave policies NIEHS offers employees. This means that more women want and are able to have a rewarding career in research, and the opportunities to make great discoveries.”

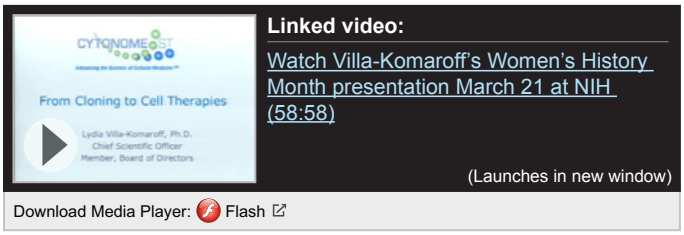
Following a recap of breakout session findings, the event concluded with a presentation by Nancy Sutley, chair of the White House Council on Environmental Quality.

Return to Table of Contents

2013 Spirit Lecture features Villa-Komaroff

By Monica Frazier

The 12th annual Spirit Lecture, “A Life in Science: From Cloning to Cell Therapies,” was presented March 22 by cell biologist Lydia Villa-Komaroff, Ph.D. Sponsored by the NIEHS Diversity Council and the Women Scientists Assembly, the Spirit Lecture Series has a history of hosting talks by outstanding women in science, each March, in honor of Women’s History Month.



Using a crafting metaphor, Villa-Komaroff described the nonlinear route she followed through academia to her current role at the cutting edge of biomedicine. “We weave a life,” she said. (Photo courtesy of Steve McCaw)

NIEHS Deputy Director Rick Woychik, Ph.D., introduced Villa-Komaroff and commented on the mission of the Spirit Lecture. “We [at NIEHS] recognize that successfully navigating today’s workplace involves balancing responsibilities for our families, our jobs, and the multiple roles we participate in, as we mentor and reach out to the wider community, all of which compete for our time and talents,” he said.

Villa-Komaroff was recently selected by the Huffington Post as one of the 50 women who shaped America’s Health, for her outstanding scientific achievements in academia, research, and business.

Accepting no barriers

Only the third Mexican-American woman ever to receive a science Ph.D., Villa-Komaroff has stopped at nothing to achieve her goals. During her postdoctoral work, she performed experiments at Cold Spring Harbor Laboratory, during the time Harvard University banned recombinant DNA research. It was this work that she brought back to Harvard and which led to the first recombinant production of mammalian insulin, an accomplishment that led to her first patent and acclaim.

Now the chief scientific officer and a board member of CytonomeST, Villa-Komaroff has successfully transitioned from academia to industry, an achievement many NIEHS trainees often wonder whether possible. Prior to joining CytonomeST, Villa-Komaroff held academic positions at major universities and research institutions, before moving into administrative roles and, ultimately, the challenging world of biomedical startup companies.

Equal opportunity criticism

Along the way, Villa-Komaroff worked for several acclaimed scientists, including Nobel laureates David Baltimore, Ph.D., as a graduate student at Massachusetts Institute of Technology, and Walter Gilbert, Ph.D., as a postdoctoral fellow at Harvard. She was insistent that choosing the right mentors was vital to her success, and that her mentors were extremely supportive during years when women in science, especially minority women, were not well accepted.

However, Villa-Komaroff made a point to emphasize that a critical mentor should not be regarded as a bad mentor. As she related her experiences to the audience, she explained, "It was not about you. It was about the work." She described her mentors as equal opportunity critics, something she strives to be in her own mentoring.

Of her own mentoring style, she said, "When undergraduates used to send me emails about spending the summer in my lab, I never answered the first email." She highlighted the need for persistence by adding, "Nobody who wasn't willing to send a second email was going to be spending any time in my lab, so just remember that."

Office of Fellows Career Development Director Tammy Collins, Ph.D., right, encouraged trainees to attend the talk. Postdoctoral fellow Staton Wade, Ph.D., center, was on hand to hear Villa-Komaroff, as was NIH Hispanic Employment Program Manager Gerard Roman. (Photo courtesy of Steve McCaw)

Also in the audience, left to right, were Diane D'Agostin, Spirit Lecture Committee member Diane Spencer, and Charlie Tate. (Photo courtesy of Steve McCaw)

Woychik introduced Villa-Komaroff and led off the question-and-answer session. (Photo courtesy of Steve McCaw)

Advice for trainees

While discussing her decisions throughout her career, Villa-Komaroff offered several pieces of advice, particularly to trainees. “You won’t get what you don’t ask for,” she said, “so aiming as high as you can is extremely important.”

Villa-Komaroff also addressed the subject of work/life balance. “I think I stopped speaking about balance a long time ago,” she said. “It’s not about balance. It’s about juggling.”

Encouraging postdocs to be open to nontraditional career paths, Villa-Komaroff continued, “We have done a disfavor to all of us, by tending to think of a Ph.D. as a degree that limits you to a particular endeavor, or field, or even job type. A Ph.D. is a degree that teaches you how to think and how to learn, and those are skills that you can apply in a very wide range of settings very, very nicely.”

If anyone can be a good example of outstanding skill adaptability, and embracing new opportunities and challenges at the highest level, Villa-Komaroff is certainly that individual.

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

Diversity Council chair Brad Collins, right, presented Villa Komaroff with a copy of the poster advertising her talk. (Photo courtesy of Steve McCaw)

The reception following Villa-Komaroff’s presentation featured Mexican fare and sweets. Chip Romeo, Ph.D., left, and Dave Malarkey, D.V.M., Ph.D., enjoyed refreshments as they talked. (Photo courtesy of Steve McCaw)

Spirit Lecture Committee members joined their guest at the refreshment tables. Shown left to right, are Suramya Waidyanatha, Ph.D., Villa-Komaroff, Veronica Godfrey Robinson, Spencer, Eli Ney, Collins, committee chair Molly Vallant, Grace Kissling, Ph.D., Roman, and Angela King-Herbert, D.V.M. (Photo courtesy of Steve McCaw)

Return to Table of Contents

In EHP editorial, Birnbaum calls new report mandatory reading

By Eddy Ball

In an editorial in the April issue of Environmental Health Perspectives, NIEHS and NTP Director Linda Birnbaum, Ph.D., applauded a new report on endocrine disrupting compounds (EDCs), "State of the Science of Endocrine Disrupting Chemicals - 2012."

Developed in the context of the Inter-Organization Programme for the Sound Management of Chemicals, the report presents an assessment by an international group of experts for the United Nations Environment Program (UNEP) and World Health Organization (WHO). NIEHS provided program support to WHO, through a cooperative agreement.

Among the authors in the working group, that developed the report and Summary for Decision-Makers, were NIEHS Program Administrator Jerry Heindel, Ph.D., and NIEHS grantees Tracey Woodruff, Ph.D., of the University of California, San Francisco, and Thomas Zoeller, Ph.D., of the University of Massachusetts Amherst. Heindel and Zoeller also served as editors. Several other NIEHS grantees contributed specific sections to the main document (see text box).

"Over the last decade, there have been significant advances in our understanding of endocrine disrupting chemicals (EDCs) — their numbers, mechanisms of actions, biological effects, and their impacts on human and wildlife health," Birnbaum wrote. "It [the new report] is an important source of data on EDCs and should be mandatory reading for everyone who is interested in protecting and improving human health."

Birnbaum has taken a lead role in NIEHS initiatives in the area of endocrine disruption and health. (Photo courtesy of Steve McCaw)

"It was a real honor to work with such a distinguished group of experts from around the world on this report on endocrine disrupting chemicals," Heindel said. (Photo courtesy of Steve McCaw)

A global problem that needs global solutions

Key concerns in the report stem from three strands of evidence:

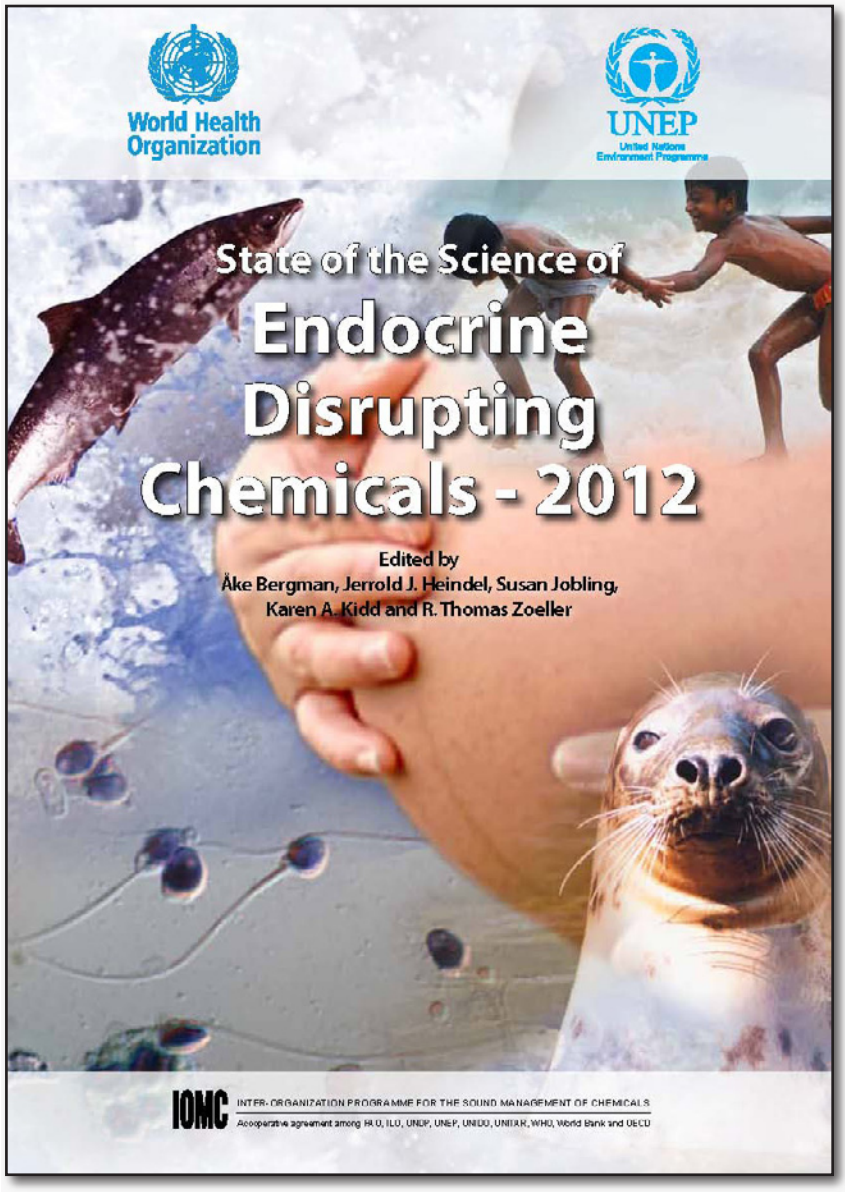
- The high incidence and increasing trends of many endocrine-related disorders in humans, not only in the U.S., but across the globe. "It is now impossible to examine an unexposed population anywhere on earth," Birnbaum observed.

- Observations of endocrine-related effects in wildlife populations. Several sentinel species, such as birds and reptiles, are undergoing losses in fertility and population that some scientists suspect are related to EDCs.

- The identification of chemicals with endocrine disrupting properties, linked to disease outcomes, in laboratory studies. "Over the last 10 years, the focus of EDC research has shifted from investigating adult exposure and disease outcomes, to examining developmental exposure and later-life disease," Birnbaum wrote.

A call for action

Like the authors of the new report, Birnbaum calls for expanding understanding of the effects of EDCs on health with more interdisciplinary research. "To improve health, it is time for environmental health scientists and toxicologists to work more closely with colleagues in endocrinology, genetics, developmental biology, epigenetics, and clinical medicine, to bring EDC research into the mainstream of science," she concluded.



Additional authors with NIEHS grant support

- Scott Belcher, Ph.D. — University of Cincinnati
- Bruce Blumberg, Ph.D. — University of California, Irvine
- Louis Guillette, Ph.D. — Medical University of South Carolina
- Philippe Grandjean, M.D., D.M.Sc. — Harvard University
- Heather Patisaul, Ph.D. — North Carolina State University
- Gail Prins, Ph.D. — University of Illinois at Chicago
- Laura Vandenberg, Ph.D. — Tufts University

Citations:

Birnbaum LS. 2013. State of the science of endocrine disruptors. Environ Health Perspect 121(4):A514.

WHO/UNEP. 2013. The State of the Science of Endocrine Disrupting Chemicals- 2012 (Bergman Å, Heindel JJ, Jobling S, Kidd KA, Zoeller RT, eds). Geneva:United Nations Environment Program/World Health Organization. Available: http://unep.org/pdf/9789241505031_eng.pdf [accessed 18 March 2013].

Return to Table of Contents

Strengthening research and community partnerships in the Gulf

More than 80 researchers and community partners gathered for the NIEHS Deepwater Horizon Research Consortia stakeholder meeting Feb. 22-23 in New Orleans. The meeting, which included broad representation from affected Gulf communities, helped community partners understand the purpose, scope, and potential outcomes of the consortia's research.

The five-year, $25 million consortia program is examining the effects of the Deepwater Horizon oil spill on human health in Gulf Coast communities, with the goal of improving community preparedness and minimizing disaster-related health impacts from factors such as stress and exposure to contaminants.

"Despite the somewhat different goals for scientists and community partners involved in the Deepwater Horizon consortia, we all want good results to come out of the research," said NIEHS Program Administrator Symma Finn, Ph.D., in her welcoming remarks. "We want to empower our community partners with more knowledge about the science, and acknowledge the great work each organization is doing to help those in their own communities."

Active community partnerships are vital to the value of the research, and face-to-face interactions give representatives, from both scientific and community perspectives, an opportunity to network, talk about their experiences, and share best practices. The meeting optimized coordination across the consortia by bringing together the investigators working on similar topics, and provided a forum for greater interaction among the scientists in the consortia, staff engaged in community outreach and research dissemination, and community partners.

Giving voice to community concerns

Claudia Thompson, Ph.D., NIEHS program lead for the consortia, provided a framework for the event, with an overview of the four consortia studies that are being led by research teams from the University of Texas Medical Branch at Galveston (UTMB), the University of Florida, Tulane University, and Louisiana State University Health Sciences Center New Orleans. These studies include active partnerships with nearly 40 community organizations across the Gulf Coast states.

Charles Wilson, Ph.D., chief scientific officer of the Gulf of Mexico Research Initiative, provided the plenary talk and an overview on the Gulf ecosystem. He described the toxicity of oil dispersant and how oil migrated post-spill. Other speakers included Elizabeth Fontham, Dr.P.H., of Tulane University, who presented on epidemiological research; Jeffrey Wickliffe, Ph.D., of Tulane University, who spoke on risk communications; and Marylee Orr of the Louisiana Environmental Action Network, who shared her experiences in community capacity building. (Photo courtesy of Andy Kane, University of Florida)

Joe Taylor, executive director of Franklin's Promise Coalition, represented one of 39 community organizations in the New Orleans meeting. "We are so very grateful for the opportunity and for the encouragement to communicate openly," Taylor said. "This has been a wonderful experience for our organization, and now I see that it's beginning to affect our grass roots community." (Photo courtesy of Andy Kane, University of Florida)

Posters and presentations by the community members highlighted the diverse activities being undertaken by local organizations in support of consortia research, and confirmed the level of commitment of these groups to the success of the program. Leaders from various organizations described training for community partners, data collection and analysis methodologies, and, importantly, outreach and educational activities.

One of the key themes of the meeting was the importance of research translation. Tap Bui, community organizer and health outreach coordinator of the Mary Queen of Vietnam Community Development Corporation, spoke of the need to communicate research activities using culturally appropriate language and formats. (Photo courtesy of Andy Kane, University of Florida)

Highly interactive working sessions highlighted the importance of community partners to the progress and success of the research. Comments during these sessions included addressing needs for:

- Sustainability of the academic-community partnerships beyond the project term.
- A greater focus on investigations of mental health outcomes in Gulf communities.
- Cultural competence when communicating with affected community members.
- Coordination with fishermen regarding messaging about seafood safety.

Additionally, some partners made clear the need for better translation of science to communities, and others expressed concern about resource needs and lack of access to services, which, although outside the purview of the consortia research, does highlight issues affecting the resilience of affected communities.

Overall, the meeting succeeded in building trust and increased the capacity for research effectiveness across the consortia.

Tracy Irani, Ph.D., director of the University of Florida Community Outreach and Dissemination Core, and Kees Elferink, Ph.D., lead researcher at UTMB, benefit from cross-consortia networking. (Photo courtesy of Andy Kane, University of Florida)

Taras Carter, senior program coordinator at Tulane University, spoke about the resources, relevant skills, and scientific literacy that community members can bring to the research table. (Photo courtesy of Andy Kane, University of Florida)

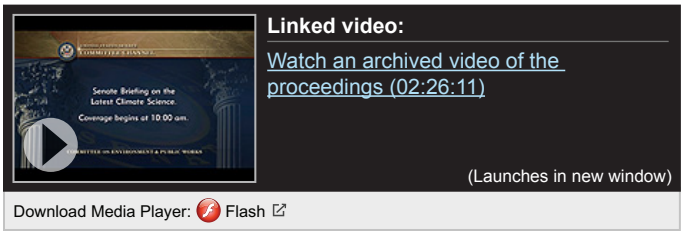
Return to Table of Contents

Balbus discusses health impacts of climate change at Senate briefing

By Paula Whitacre

"We need to follow the science," stated Sen. Barbara Boxer, D-Calif., chairman of the U.S. Senate Committee on Environment and Public Works, at the opening of the "Senate Briefing on the Latest Climate Science" Feb. 13 in Washington, D.C.

The session brought together four climate change experts, including NIEHS Senior Advisor for Public Health John Balbus, M.D. Rather than a formal briefing, the panelists each gave short prepared remarks, followed by an extensive question-and-answer period with members of Congress and their staffs.



Balbus is the NIEHS lead for climate change and global health initiatives. (Photo courtesy of Steve McCaw)

In addition to Balbus, participants were James McCarthy, Ph.D., professor of biological oceanography at Harvard University; J. Marshall Shepherd, Ph.D., president of the American Meteorological Society and director for the Program in Atmospheric Sciences at the University of Georgia; and Donald Wuebbles, Ph.D., professor of atmospheric science at the University of Illinois.

Balbus was invited in his roles as the U.S. Department of Health and Human Services principal to the Global Change Research Program (GCRP), co-chair of the interagency Climate Change and Human Health Group under the GCRP, and lead author of the health chapter of the National Climate Assessment, which was released in draft in mid-January.

Now in her third term as a U.S. senator, Boxer is known for her concern for the environment. (Photo courtesy of Barbara Boxer)

Climate change and the implications on human health

In his prepared remarks, Balbus drew from the health chapter of the Assessment:

- Climate change threatens human health and well-being in many ways, including changes in water and food supplies, and inundation of low-lying coastal areas. Some of these impacts are already being felt in the United States. Drawing on evidence that included an NIEHS-funded study, he explained, "In addition to hot days causing stress, the extent of summertime temperature swings that people with heart disease and diabetes are exposed to is very important."

- Climate change often acts as a multiplier of existing health threats. He highlighted research on how climate change can worsen pollen release, air pollution, heat stress, and the incidence and range of infectious diseases. "People with underlying diseases, at certain life stages, or with other social risk factors, are more vulnerable," he said.

- Measures to reduce emissions of heat-trapping gasses or improve community resilience can have significant and immediate health benefits. Referring to NIEHS-supported research published in the Lancet, Balbus emphasized the positive benefits to human health from decreased air pollution, increased physical activity, and changes in agricultural practices, among other strategies for reducing the impact of climate change.

Congressional reaction and discussion

The senators and representatives expressed their appreciation to the scientists for their direct and straightforward comments. "Your voices are key," said Boxer. She added that a combination of scientific credentials and the ability to talk understandably to non-scientists is essential in the policymaking process.

The scientists fielded a range of questions, from the current situation to their projections for the end of the century. Sen. Mark Udall, D-N.M., asked about how to take advantage of teachable moments, such as those created by wildfires and drought in his state, to communicate with citizens so they, in turn, press their elected leaders to take action.

In response to Udall and to Rep. Henry Waxman, D-Calif., Balbus referred to public health research on risk communication and behavior change, including presentations at a workshop in January for NIH and Centers for Disease Control and Prevention grantees (see story). "The research shows that what motivates people to change is not to just scare them, but a more positive call to a greater good," he said. He noted that investing in research into how people are motivated to change their behaviors has payoffs for public health, broadly, and for climate change-related health impacts, specifically.

Boxer picked up on Balbus' point about the other positive results that can occur when taking action to reduce carbon, such as improved air quality, as other pollutants decrease. "The bottom line is there are cobenefits to public health," she said. "That is huge."

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

Return to Table of Contents

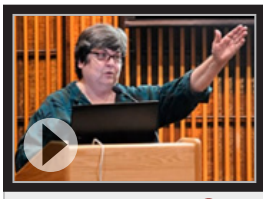
Balancing economic development with air pollution curbs

By Carol Kelly

Balancing the goals of boosting economic development and curbing residential air pollution from goods movement may be difficult, because health effects from related environmental exposures may not be well known. Goods movement is the transport of products from their location of manufacture, harvest, or entry to final retail destination.

A guide to attaining such social equilibrium is available in a new environmental justice case study by NIEHS grantees. The study, published Feb. 19 in the journal Environmental Justice, chronicles development and progress of THE (Trade, Health, Environment) Impact Project, a community-academic partnership formed to address health effects associated with air pollution from traffic through the massive Los Angeles and Long Beach Ports complex.

"As part of THE Impact Project, we recognized the disproportionate impacts in living near ports and goods movement facilities for lower-income, minority residents," said Andrea Hricko, professor of clinical preventive medicine and director of community outreach and engagement for the NIEHS-supported Southern California Environmental Health Sciences Center at the University of Southern California (USC).



Linked video:

Watch a video tribute to Hricko celebrating her selection as the winner of the 2012 Environmental Health Champion Award by the Physicians for Social Responsibility of Los Angeles (03:35) (Launches in new window)

Download Media Player: Flash

One of THE Impact Project's neighborhood assessment teams, called A teams, count truck traffic in a park next to a congested freeway in Long Beach, Calif. (Photo courtesy of Andrea Hricko)

Helping residents find a voice

Turning community residents into science-savvy advocates, for reducing environmental exposures in their neighborhoods, is a notable project success. Community-based participatory research (CBPR) was used to form and train neighborhood assessment teams in understanding health effects from traffic pollution exposure and then identifying community hot spots, such as locations where children are exposed to high-volume truck traffic. After training, teams used hand-held, real-time particle counters, to measure ultrafine particle concentrations. Empowered community members took a leading role as evidence-based advocates, presenting their findings to policymakers.

"THE Impact Project put a face on the statistics, by humanizing data and helping change the debate from one solely focused on economic gains to one inclusive of mitigating health effects that disproportionately impact low-income communities of color," said Analilia Garcia, Dr. P.H., the study's lead author, who is now a senior community health planner in Santa Clara, Calif. "Furthermore, the regional collaboration strengthened the partnership's work, building a stronger case for the impact of goods movement."

"CBPR works to improve both distributive justice and also procedural justice, through which community partners get a seat at the decision-making table, and stay at the table, helping to inform decisions that affect their lives and communities," said Meredith Minkler, Dr.P.H., a co-author and professor of health and social behavior at the University of California, Berkeley, School of Public Health.

Linked video:

Watch as Minkler describes CBPR and its power to influence public health policy (02:46)

(Launches in new window)

Download Media Player: Flash

Hricko, center, leads a training session with local residents, who are often Latina women whose children have asthma. (Photo courtesy of Andrea Hricko)

Founded in 2006, THE Impact Project partners — USC, Occidental College, and four community-based advocacy groups — worked together to colearn and build capacity in one of the world's largest international trade sites.

Collaboration among community members and scientific investigators

"THE [Impact] Project shows the value of bidirectional communication between community and scientific investigators," said Hricko. "The community groups understand the research findings much better through our engagement, but our scientists also understand the on-the-ground environmental health risks in the community."

Through its accomplishments and longevity, THE Impact Project has garnered local and national attention, with its members serving as advisors to, and resources for, other community organizations facing environmental injustices.

"It shows how community-based organizations can become key figures in policy debates and positive health change at a regional level, rather than just a local level," said Nina Wallerstein, Dr.P.H., a co-author and director of the Center for Participatory Research at the University of New Mexico.

However, THE Impact Project was dealt a blow March 7, when Los Angeles harbor commissioners approved the Southern California International Gateway, a $500 million rail yard that could generate an estimated 22,000 port-related jobs, but also drive more air pollution toward nearby schools, parks, and low-income neighborhoods. Two community partners plan to appeal the decision to the Los Angeles city council, which has not yet approved the rail yard.

"A lesson we've learned from the rail yard decision is that even more work is needed to inform policymakers about environmental health research findings, as they make land use decisions," said Hricko.

Citation: Garcia AP, Wallerstein N, Hricko A, Marquez JN, Logan A, Nasser EG, Minkler M. 2013. THE (Trade, Health, Environment) Impact Project: A Community-Based Participatory Research Environmental Justice Case Study. Environmental Justice 6(1):17-26.

More about traffic-related particle pollution and health effects

The haze that forms when millions of tiny solid and liquid particles blur sunlight is a visual clue that people may be breathing particle pollution. Although these particles are created in different ways and composed of different compounds, most industrial-origin particles are generated through burning fossil fuels, such as in diesel-powered and gasoline-powered vehicles and equipment. The tiny particles in diesel exhaust can pass through the lungs into the bloodstream, carrying heavy metals, sulfates, and other chemicals.

In 1988, the International Agency for Research on Cancer (IARC), a part of the World Health Organization, classified diesel exhaust as probably carcinogenic to humans. The California Air Resources Board classified diesel as a strong cancer risk in 1998, and passed a number of regulations to reduce the public's diesel pollution exposure from such sources as trucks, ports, and agricultural equipment. In June 2012, IARC declared that exhaust from diesel engines can cause cancer.

"The scientific evidence was compelling, and the working group's conclusion was unanimous — diesel engine exhaust causes lung cancer in humans," said Christopher Portier, Ph.D., chairman of the IARC working group, in a statement. "Given the additional health impacts from diesel particulates, exposure to this mixture of chemicals should be reduced worldwide."

In addition to causing lung cancer, strong evidence shows that particle pollution can increase the risk of heart disease, and interfere with lung development and function. A growing body of evidence suggests breathing pollution from heavy traffic may cause asthma in children. Nearly six million people in the United States live in an area with unhealthy year-round levels of particle pollution, according to the American Lung Association's 2012 State of the Air report.

(Carol Kelly is a health communication specialist with MDB Inc., a contractor to the NIEHS Division of Extramural Research and Training.)

Return to Table of Contents

Panel highlights climate change science that can improve global health

By Paula Whitacre

Efforts around the world to reduce the impacts of climate change on infectious and noncommunicable diseases, worldwide, were explored in a plenary panel convened by NIEHS Senior Advisor for Public Health John Balbus, M.D., at a conference of the Consortium of Universities for Global Health (CUGH) March 16 in Washington, D.C.

Recognizing the urgency

In introducing the panel, Balbus referred to the most prevalent global health problems listed in the recently published Global Burden of Disease Study 2010, noting that both increases in short-term weather variability and long-term climate change can exacerbate chronic diseases or shift patterns of vectors affecting certain infectious diseases.

For some in the global health field, Balbus acknowledged, preoccupation with urgent health crises may lead to considering climate change as something outside of their areas of concern that can be dealt with in the future. He asked the audience to avoid this kind of complacency and recognize the urgency of the effects of changes in weather patterns.

"Climate change is occurring and it's having an impact on the kinds of diseases we now take care of," Balbus said. "The session was designed to show how bringing in scientific data and tools, related to climate change and meteorology, can enhance health programs."

NIH plays a prominent role at global health conference

The fourth annual meeting of the Consortium of Universities for Global Health brought together health professionals and students primarily from universities, but also from agencies and organizations in the U.S. and globally.

In addition to NIEHS, the National Cancer Institute and the Fogarty International Center were among the co-sponsors of the event held Mar. 14-16 in Washington, D.C. Several sessions highlighted the role of NIH in global health, including a presentation by NIH Director Francis Collins, M.D., Ph.D.

Collaboration and local solutions

Two common themes emerged in the discussions — the need to work across health, meteorology, agronomy, and other disciplines; and that while climate change is global, impacts and solutions are local. Demonstrating the multidisciplinary nature of addressing climate-related health impacts, the panel consisted of an epidemiologist, two engineers, and a biologist.

Kristie Ebi, Ph.D., a leader in the field of climate change health adaptation, noted that understanding risks involves three factors — the specific impact, such as flooding, heat waves, or drought; who or what is exposed

to it; and underlying vulnerabilities, which are very context-dependent. She called for transitional and transformational learning that can lead to system-wide changes in approaches to complicated problems.

Rao Aiyagari, Ph.D., senior advisor for research development and scientific operations at the Public Health Foundation of India, discussed two examples — extreme heat in west India and the impact of indoor air pollution on acute respiratory conditions. He said that research and effective solutions require collaboration across institutions, agencies, and regions. “It is necessary for public health knowledge to be given to climate change professionals, and climate change knowledge to be given to public health professionals,” he concluded.

Pamela Anderson, Ph.D., director general of the International Potato Center (IPC) in Lima, Peru, spoke about food security. Without interventions, climate change is anticipated to significantly decrease production of wheat, rice, and potatoes, the world’s three most consumed crops. She said that IPC has three roles related to climate change — climate-proofing through crop improvement and breeding; preserving biodiversity of the 5,000 varieties of native potatoes in a gene bank and natural habitats; and mitigation research. Food security, she stressed, requires looking for local solutions and applying appropriate options.

Gueladio Cisse, Ph.D., environmental scientist at the Swiss Tropical and Public Health Institute, described the water, health, and climate change project he directs in four river-adjacent West African cities. Noting that the process was as important as the outcome, he pointed to successes that include an agreement on the project framework and focus, collection of local health and climate data, and a bridge to policymakers. Local and national authorities are enthusiastic about the research, but adaptation plans need to be developed and funded.

Questions for the panelists included their perspectives on partnering with the private sector and the role of local data.

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

Members of the Climate Change and Global Health: Using Science to Protect Populations panel agreed on the urgency of the climate change issue, and the need to collaborate across disciplines and with local communities, to have an impact on health. Shown, left to right, are Balbus, Ebi, Anderson, Cisse, and Aiyagari. (Photo courtesy of Paula Whitacre)

Return to Table of Contents

Outreach workshop keeps teachers engaged

By Sheila Yong

The NIEHS Rodbell Auditorium was abuzz with activity and laughter March 11, as 21 science teachers and educators joined in the Rx for Science Literacy workshop organized by the NIEHS Office of Science Education and Diversity, in partnership with the North Carolina Association for Biomedical Research (NCABR). NCABR is a nonprofit organization that promotes science education and biomedical research throughout the state. Participants of this workshop earn credit towards their continuing education and certification.

Besides welcoming the participants to the Rx for Science Literacy workshop, Williams also encouraged them to provide comments and feedback on topics they would like to see presented at future NCABR programs. (Photo courtesy of Steve McCaw)

"We are grateful to NIEHS for their donation of resources and staff time, which allows us to provide you with materials for your classrooms, as you talk to your students about biomedical research," said NCABR Director of Programs Regina Williams in her opening remarks. As she introduced the attendees to the workshop's agenda, Williams also highlighted the various presentations featuring scientists at NIEHS.

Following Williams' introduction, NIEHS Program Analyst Liam O'Fallon, of the Division of Extramural Research and Training, gave an overview of the research goals of the Institute. His presentation also detailed various printed and online resources available through NIEHS, which teachers can use to introduce their students to environmental health research.

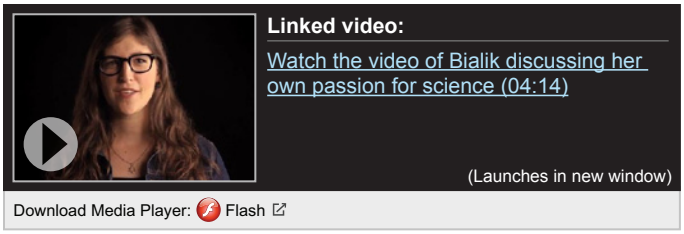
O'Fallon creatively used Johnny the crossing guard as an example of how exposure to various environmental elements may impact human health, and described the NIEHS mission to understand the outcome of such exposures. (Photo courtesy of Steve McCaw)

A morning of hands-on fun

The participants spent the first half of the workshop engaging in hands-on activities, under the guidance of Pamela Lovin, educational consultant from NCABR. To simulate the classroom environment, Lovin had participants work in pairs and groups to complete the assignments.

In the midst of fun and laughter, the participants exercised their observational and analytical skills to solve problems that Lovin put forward, and gained insights into how they could implement these activities in their classrooms.

One such activity required attendees to picture the appearance and characteristics of a scientist, and some volunteered to describe their drawings to the rest of the participants. The drawing that stood out came from teacher Jill Messer of Piedmont High School, who displayed her depiction of Sheldon Cooper, the uptight physicist on the popular sitcom "The Big Bang Theory." Her presentation was later complemented by a video Lovin played of actress and neuroscientist Mayim Bialik.



Overall, the goal of Lovin's activities was to help teachers instill curiosity and passion in their students about science. "Your students don't have to be extremely intelligent to become scientists. They just have to be curious and willing to learn new things," she said.

A day full of ideas on science learning

One of only four male participants of the Rx for Science Literacy workshop, teacher Brandon Staton of Thomasville High School appreciates the opportunity to learn more about how he can engage his students in biomedical research and promote diversity in the scientific workforce. "I think the workshop is awesome. Not only can we visit a science building where research is being done, but we also get some good lesson ideas that we can take back to our classrooms," he exclaimed.

Staton said that workshops like this are beneficial for all teachers who strive to educate their students about the importance of science. Although males often outnumber their female counterparts in scientific careers, Staton feels that more can be done to encourage female, as well as minority, students. "You don't see a lot of female and minority scientists. We, as teachers, are trying to change that," he commented. Staton said he plans to apply what he learned at the workshop in his classroom and to engage his students in the fun, yet educational, scientific activities.

NIEHS behind the scenes

The afternoon section of the workshop began with a presentation by Veterinary Staff Scientist David Kurtz, D.V.M., Ph.D., on the humane use of animals in environmental research. Following his talk, the participants, led by Kurtz and Veterinary Medicine Section Chief Terry Blankenship-Paris, D.V.M., toured the Comparative Medicine Branch facilities.

Next to speak was Ruth Lunn, Dr.P.H., director of the NTP Office of the Report on Carcinogens (RoC). In her presentation titled "Environmental Exposures and Cancer Hazards," Lunn introduced the teachers to the RoC, a congressionally mandated document that discusses substances that cause, or are anticipated to cause, cancer. She also described the procedures required for the classification of these substances and how the general public can participate in the process.

Humphrey Yao, Ph.D., lead researcher in the NIEHS Reproductive Developmental Biology Group, concluded the workshop with his presentation on "Sex, Arsenic, and the Environment: How Maternal Exposure Affects the Reproductive System of the Offspring." At the start of his presentation, Yao expressed his gratitude to the participants for their efforts in teaching science to the next generation. "All of you, as science educators, are in a very important position, by helping us communicate the importance of scientific research to your students and the community at large."

During his talk, Yao presented recent findings from his group on the effects of *in utero* arsenic exposure on body weight and the onset of puberty. His presentation raised several questions among the attendees who wanted to understand the effects of long-term arsenic exposure and how they can be minimized.

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

Much like a teacher in her classroom, Lovin first laid down the ground rules for her session of the workshop, before engaging the attendees in various hands-on activities. (Photo courtesy of Steve McCaw)

Lunn guided the attendees through the process of compiling the Report on Carcinogens, which provides information to the public on substances that have been shown to cause, or may result in, cancer. (Photo courtesy of Steve McCaw)

Left to right, Evelyn Lynge of the Onslow County Council for Women, Staton, and teacher Crystal Payton-Demry of Kinston High School listened attentively to Yao's presentation. Staton said the workshop provided him with many ideas and resources, and he looks forward to sharing them with his students (see text box). (Photo courtesy of Steve McCaw)

Messer proudly showed her drawing of Sheldon Cooper, a theoretical physicist on the hit American sitcom "The Big Bang Theory." Her witty presentation drew laughter from everyone in the auditorium. (Photo courtesy of Steve McCaw)

Left to right, teachers Abria Vodenichar of Bethany Community Middle School, Janet Brower of Weddington High School, and Matthew Boyd of Clinton City Schools were deep in discussion during one of the group activities. (Photo courtesy of Steve McCaw)

Along with sharing his research findings, Yao also filled his presentation with information relevant to the well-being of the community. In the midst of his wit and jokes, he drove home the solemn point that the arsenic level in some drinking water, today, is in fact sufficient to cause the phenotypes his group had observed in their laboratory mice. (Photo courtesy of Steve McCaw)

Return to Table of Contents

Family-friendly pilot project offers options for IRTA trainees

By Eddy Ball

About half of the trainees working at NIEHS in established research programs could potentially qualify for an NIH pilot program known as Keep the Thread.

Intramural Research Training Award (IRTA) fellows may be able to negotiate flexible work arrangements with their supervisors and the Office of the Scientific Director, to accommodate family care needs, such as the birth of a child or the care of a family member. Following their standard eight weeks of paid parental leave, or for situations not covered by parental leave, IRTA fellows may be able to modify the duration of their training time at NIEHS, so they can continue to pursue their career goals, by keeping the NIH training thread intact.

"Keep the Thread offers the kind of support I wish had been available when I was a young mother pursuing a career in science," said NIEHS and NTP Director Linda Birnbaum, Ph.D., who was part of the working group that developed the pilot project. "I'm glad to see so much support for the project here and at NIH in Bethesda, and I hope it helps young scientists balance work and family during critical periods in their training."

According to Collins, NIEHS Scientific Director Darryl Zeldin, M.D., fully supports the new program. "Darryl has even advertised this [Keep the Thread] several times himself," she said. (Photo courtesy of Steve McCaw)

Making an informed decision

Launched by the Women in Biomedical Careers Committee of the NIH Intramural Research Program, Keep the Thread is a three-year pilot program to increase flexibility for NIH intramural fellows who need alternative career development schedules. The goal of the program is to encourage trainees to stay connected to the NIH community during times of intense personal or caregiving needs, in order to facilitate eventual re-entry into full-time research.

Taking an extended leave of absence or temporarily reducing effort could have unintended consequences for a trainee's career. Collins explained that trainees should meet with a career counselor and schedule one or more follow-up meetings. OFCD also offers several materials for trainees and their supervisors who are considering the Keep the Thread option, including a detailed checklist for outlining the agreement.

"While this program isn't for everyone, it has the potential to help people better balance work and life during their time as IRTA trainees," Collins said.

For more information, IRTA trainees and their supervisors should contact Collins by email at tammy.collins@nih.gov or by telephone at 919-541-3344. Detailed information about available options, what forms need to be filled out, and who is eligible, is also available on the NIH intranet site at http://sourcebook.od.nih.gov/prof-desig/Keep_the_Thread_2012.docx.

Eligibility depends on type of training award

As intriguing as the summary of the new program sounds, Director of the NIEHS Office of Fellows' Career Development (OFCD) Tammy Collins, Ph.D., is eager to underscore the caveats, and help potential participants fully understand the pilot program.

"Because of visa requirements, foreign nationals on J-1 visas aren't eligible to take part in the program, and research fellows, who are term-limited federal employees, already have access to NIH programs for what are known as full-time equivalencies, or FTEs," Collins explained. "But, even though they can't reduce their effort under Keep the Thread, visiting and research fellows can still negotiate flexible full-time schedules and telework options with their supervisors."

According to information about the program, Keep the Thread is an option for IRTA fellows, not an entitlement, and there can be significant financial trade-offs to consider.

Stopping or slowing down the training clock

Negotiating a flexible schedule under Keep the Thread doesn't increase the amount of stipend a trainee can receive as an IRTA, only the period of time over which that stipend may be prorated. IRTA trainees can receive up to five years of support, but, with Keep the Thread, the option exists to receive that five years of support over a longer period of time for trainees who gain approval for a temporary reduction of effort.

In addition to temporary reduction of effort to a level equal to or greater than 40 percent of full time, Keep the Thread options include flexible scheduling, telework, working as a special volunteer, and fee-for-service as a contractor. The length of time permitted varies with each option.

Working a reduction in effort schedule will affect pay and may impact benefits for IRTA trainees. In order to retain full coverage of health benefits, fellows must work a minimum of 80 percent, or 32 hours per week.

With a temporary reduction below that level to 40 percent or greater, fellows must contribute a percentage of health costs equivalent to their percent reduction of effort. Special volunteers pay for health insurance out of pocket, and contractors are not eligible to participate in NIH health insurance plans.

Return to Table of Contents

Smaller presence at SOT, but big enthusiasm for science

By Robin Mackar

Although the NIEHS and NTP presence at this year's Society of Toxicology (SOT) annual meeting March 10-14 was much smaller than usual due to budget concerns, enthusiasm for science was still in abundance.

San Antonio was the place to be for those who wanted to hear the latest toxicology findings, learn about funding and training opportunities, and personally meet some of the NIEHS and NTP staff attending and participating in the meeting.

Before the official meeting even kicked off, staff members were busy serving on committees planning for next year's conference, setting up posters and exhibits, and teaching continuing education courses.

Funding issues

At the Meet the Director symposium on March 11, Linda Birnbaum, Ph.D., director of both the NIEHS and NTP, updated SOT attendees on the current federal budget scenario, which she acknowledges is something that has been changing on an almost daily basis.

Birnbaum talked about steps being taken at NIH to prepare for the sequestration. "As of March 1, the federal government is operating under a sequestration, which means a 5 percent cut for NIH," Birnbaum said. She discussed how the payline for grants at NIEHS would likely have to drop, resulting in fewer new grants being funded. Birnbaum encouraged attendees to continue their conversations with NIEHS program staff to keep abreast of available funding announcements and opportunities.

Birnbaum also used her time to update attendees on happenings at the Institute, including progress toward developing cross-cutting implementation plans to help NIEHS reach its overall strategic goals.

Resource room

One of the most popular spots for new investigators, as well as long-standing grantees, was the centrally located NIH resource room.

"The funding room was always busy," said Annette Kirshner, Ph.D., program administrator in the NIEHS Cellular, Organ, and Systems Pathobiology Branch of the Division of Extramural Research and Training (DERT). Kirshner and others in DERT, including Janice Allen, Ph.D., from the Scientific Review Branch, worked with SOT to host the room and a brown bag luncheon, so new investigators could become familiar with the NIH peer review grant process. DERT staffed the room for two days, providing one-on-one consultation time with researchers who had questions about NIH funding and training opportunities.

Another popular session was the symposium chaired by Paul Foster, Ph.D., of NTP, and Earl Gray, Ph.D., of the U.S. Environmental Protection Agency. It was standing room only for the "Nonmonotonic Dose-Response Curves and Endocrine-Disrupting Chemicals: Fact or Falderal?" session, which also featured Birnbaum.

Birnbaum, left, always made time to talk science with SOT attendees. (Photo courtesy of Robin Mackar)

Nigel Walker, Ph.D., NTP deputy division director for science, left, and Mary Wolfe, Ph.D., NTP deputy division director for policy, right, set time aside to talk to a delegation from China about NTP key activities and how NTP is organized. (Photo courtesy of Denise Lasko)

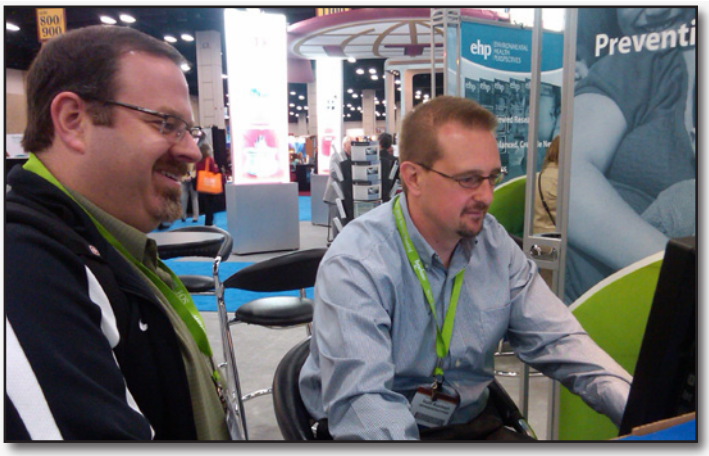
Ray Tice, Ph.D., chief of the NTP Biomolecular Screening Branch, right, converses with Outstanding New Environment Scientist awardee Vishal Vaidya, Ph.D., of Harvard, about NTP efforts, through Tox21, to link chemicals, genes, pathways, and disease. (Photo courtesy of Robin Mackar)

Many postdocs stopped by the popular, consolidated NIEHS, NTP, and Environmental Health Perspectives (EHP) exhibit to talk with staff about available positions in NTP. (Photo courtesy of Robin Mackar)

There were always stimulating conversations going on in the well-attended resource room. Above, NIEHS Program Administrator Carol Shreffler, Ph.D., right, meets with Ezdihar Hassoun, Ph.D., of the University of Toledo. (Photo courtesy of Robin Mackar)

Tammy Collins, Ph.D., right, who heads the NIEHS Office of Fellows' Career Development, shared her experience of being a postdoc with others who stopped by the exhibit. Collins walked prospective applicants through the process of applying for laboratory positions at NIEHS. (Photo courtesy of Robin Mackar)

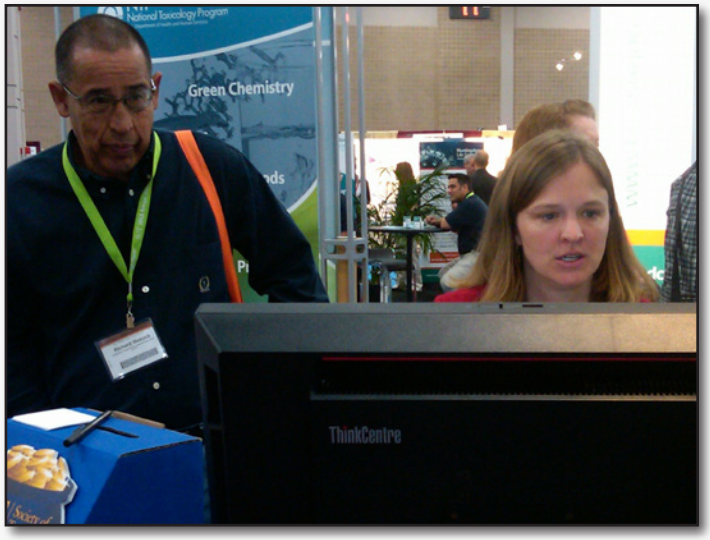
NTP Toxicology Branch Chief Paul Foster, Ph.D., was all smiles, after his talks on low-dose were completed. (Photo courtesy of Robin Mackar)



Scott Auerbach, Ph.D., right, of the NTP Biomolecular Screening Branch, gave hands-on demonstrations of the DrugMatrix® database and ToxFX® reporting system, at the exhibit space. (Photo courtesy of Robin Mackar)

NTP biologist Laura Hall, right, spent many hours proudly showcasing the capabilities of the Chemical Effects in Biological Systems database, based at NIEHS. (Photo courtesy of Robin Mackar)

EHP contract staff Mary Collins, Ph.D., right, talked a potential author through some editorial suggestions. (Photo courtesy of Denise Lasko)



Abee Boyles, Ph.D., center, demonstrated some of the Web-based tools that the NTP Office of Health Assessment and Translation (OHAT) has brought forward for systematic review. Boyles and Andrew Rooney, Ph.D, also of OHAT, presented the tools and concepts of systematic review, at a well-attended exhibitor-hosted session on March 12. (Photo courtesy of Robin Mackar)

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

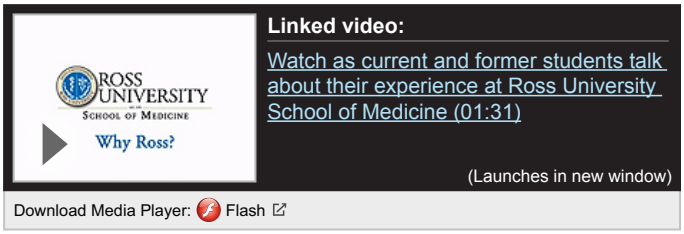
Return to Table of Contents

Former NIEHS research fellow enters medical school

By Robin Arnette

As a child, former NIEHS research fellow Quiana Childress couldn't have imagined the twists and turns her life would take when she decided she wanted to be a doctor, but on May 6, she will be closer than ever to becoming a physician.

That's because Childress will begin the first day of coursework at Ross University School of Medicine (RUSM) in the West Indies as a member of its 2013 incoming summer class. Her acceptance into medical school marks the end of an arduous journey, but the beginning of a potentially long, fulfilling career in medicine.



Will to succeed

Childress grew up in a large family where money was tight. To help out, she worked after school as a Certified Nursing Assistant (CNA) and decorated birdhouses. Eventually, Childress found herself homeless, but even these circumstances didn't deter her. She received good grades in school, tutored elementary kids, and served as captain of her varsity basketball team.

After graduating from high school, she spent a year completing a Licensed Practical Nursing (LPN) program, which allowed her to pay her way through college at the University of Arkansas at Pine Bluff (UAPB). Working as an LPN at an all-male maximum security prison and majoring in biology both presented challenges, but Childress' resolve and excellent time management skills permitted her to also volunteer for local and national organizations, help charter two student groups on campus, and participate in undergraduate research programs offered by the University of Alaska Anchorage, Yale University School of Medicine, and the National Aeronautics and Space Administration. Through it all, she maintained a 3.9 GPA.

"As a first-generation, working college student, I encountered bumps along the road," Childress said, "but each new experience strengthened me and compelled me to keep pressing on."

When Childress graduated summa cum laude from UAPB in May 2010, she had the honor of hearing First Lady Michelle Obama mention her name during the commencement address. Mrs. Obama used Childress' life story to inspire others to never give up, no matter the adversity.

"The prayers and help from countless family, friends, mentors, and supporters have allowed me to make it this far in life, and I am overjoyed that RUSM will allow me the opportunity to pursue my dreams of becoming a physician," Childress said. (Photo courtesy of Crafte Eye Photography)

Research and medicine

Childress spent the next two years doing biomedical research, both at NIEHS and at Meharry Medical College in Nashville, Tenn. During her time at the Institute, Childress worked with NIEHS Acting Clinical Director Stavros Garantziotis, M.D., investigating lung transplant rejection. At Meharry, she earned a graduate certificate in health sciences and studied how vascular signaling regulates nitric oxide production. While Childress may engage in some research at RUSM, her sights are set on mastering the information needed to land a good residency program.

Standing on the shoulders of others

As a testament to her superb work ethic, Ross University selected Childress to receive the Eliza Anna Grier Scholarship, named in honor of the first African-American woman licensed to practice medicine in Georgia. Grier was an emancipated slave who took 14 years, alternating years of picking cotton and attending school, to obtain her M.D. from the Woman's Medical College of Pennsylvania. When she finished in 1897, Grier returned to her hometown of Atlanta to provide medical care to the city's African-American community.

The Grier scholarship will cover $2,000 of the cost of tuition per semester and is renewable as long as Childress is continuously enrolled and maintains a minimum 3.0 cumulative GPA.

According to Carey James, associate dean and director of admissions at RUSM, the school has had more graduates obtain U.S. residencies over the last five years than any other medical school in the world. He attributes most of the credit to students who are relentless in the pursuit of their career aims.

"A talented student like Quiana perfectly fits the profile of an RUSM student, who has both immeasurable potential, as well as a strong personal commitment to achieving her goals, regardless of the obstacles in her way," James said. "We are proud to welcome her to the RUSM community."

Return to Table of Contents

Career fair to focus on the dynamic nature of biomedical careers

By Ashley Godfrey

The 16th annual NIEHS career fair will once again be held at the U.S. Environmental Protection Agency (EPA) Research Triangle Park, N.C., campus on Friday, April 26.

This year's event features a keynote address, "A Crook in the Road: A Real World Path in Bioscience Entrepreneurship," by Patricia Beckmann, Ph.D., former executive director of the Oregon Translational Research and Development Institute and founder of the consulting company BioStrategy, LLC. One of the central themes for this year's fair is that today's biomedical science careers are more likely to follow a zigzagging path to success.

"This is something that I hope Dr. Beckmann will emphasize and will be highlighted by a career transitions panel with scientists who have successfully made moves between academia and industry. There will also be workshops focused on leadership skills and recognizing and articulating transferable skills that are useful across career types," explained Staton Wade, Ph.D., one of two co-chairs in charge of planning this year's event.

Wade is a postdoctoral fellow in the Chromatin and Gene Expression Group in the NIEHS Laboratory of Molecular Carcinogenesis. (Photo courtesy of Steve McCaw)

Beckmann brings nearly 25 years' experience in biotech that includes postdoctoral experiences as a Fulbright scholar and a visiting scientist at the National Cancer Institute (NCI), many dozens of published papers and patents, and a long list of jobs from drug, law, and venture capital firms, to state economic development organizations.

Co-chair responsibility is shared by Kymberly Gowdy, Ph.D., a postdoctoral fellow in the Clinical Investigation of Host Defense Group in the NIEHS Laboratory of Respiratory Biology. (Photo courtesy of Steve McCaw)

Paving the road to success

The career fair is organized and run by a committee of NIEHS and EPA trainees, and is one of the area's most highly attended career fairs, drawing young scientists from many of the surrounding universities. The goal is to provide workshops and panel sessions, to give these young scientists the skills and connections they need for career satisfaction and success.

Reflecting the ever-changing climate in bioscience careers today, this year's panels lean toward many nontraditional, nonbench careers, and are focused on a particular type of job or interest area, such as science policy, public health, heading up a lab, and education. The planning committee added more workshops this year, and put panels and workshops together running concurrently in one-hour sessions. Workshops include a variety of career skills from setting career goals and preparing for an interview, to management and leadership skills for scientists.

The planning committee worked very hard to make changes to this year's fair, based on prior years' feedback. "We have tried to incorporate epidemiologists on the panels, especially in the areas of science policy and public health, and we have expanded the popular CV/resume reviews to about twice as many slots as last year," explained Wade.

Registration opened on March 18th and will close once the event is full. Interested trainees should secure their spot, as soon as possible, for a day focused on helping build a path to success. For more information about the career fair, go to http://tools.niehs.nih.gov/careerfair/index.cfm.

(Ashley Godfrey, Ph.D., is a postdoctoral fellow in the Molecular and Genetic Epidemiology Group in the NIEHS Laboratory of Molecular Carcinogenesis.)

Trainees get to meet and greet people from other institutions, catch up with former colleagues who have made the big transition, and gain a new perspective on the job market. (Photo courtesy of Steve McCaw)

The career fairs consistently draw a capacity audience of young scientists eager to network and learn. (Photo courtesy of Steve McCaw)

This year's fair will host a number of local companies and organizations eager to interact with young scientists. (Photo courtesy of Steve McCaw)

Much of the Biomedical Career Fair is devoted to sector- and profession-focused panels where representatives give brief presentations and answer questions. NIH Human Resources specialist Angela Davis, above, participated in a panel on federal government employment. (Photo courtesy of Steve McCaw)

Return to Table of Contents

Science Notebook

Falk lecture highlights the importance of microbes in chronic disease

By Robin Arnette

A rainforest offers the millions of species that inhabit it a home that provides for their every need. This lush, green landscape maintains its ecological balance, because each organism contributes to the rainforest's stability. But, what happens if you remove one species from that environment? The habitat experiences changes that negatively affect the entire community.

According to infectious disease epidemiologist Julie Parsonnet, M.D., each person is his or her own rainforest. Getting rid of one microorganism, out of the millions that live in and on us, collectively known as the microbiome, changes how this unique ecology develops. Understanding how the microbiome affects human health represents a new frontier of medicine, and research from Parsonnet and others has helped to uncover the role of bacteria in everything from cancer and diabetes to food allergies and obesity.

Parsonnet is a professor of medicine in the Division of Infectious Diseases and Geographic Medicine and the Division of Epidemiology at Stanford University School of Medicine. (Photo courtesy of Steve McCaw)

Parsonnet discussed her work as the featured speaker March 19 for the 2013 Hans L. Falk Memorial Lecture. Stephanie London, M.D., Dr.P.H., and Walter Rogan, M.D., co-hosted the seminar.

"Dr. Parsonnet has made landmark contributions to understanding the link between infections and chronic disease," London said. Parsonnet and London were residents together at Massachusetts General Hospital in Boston. (Photo courtesy of Steve McCaw)

The gut is our second brain

Parsonnet said the microbes that live on us constantly communicate with our cells, but the ones that exist in the human gastrointestinal tract may be responsible for the old adage, you are what you eat. If you like to eat sugary or salty snacks, you will enrich your gut with microbes that want those foods. If you stop eating them, your gut bacteria may send signals to your brain telling you to eat more of what they like.

"You may be saying I want the garden salad, but your microbiome is saying, 'I'll take the cheeseburger and fries,'" Parsonnet remarked.

One of the gut microbes Parsonnet has studied is the stomach bacteria *Helicobacter pylori (H. pylori)*, which causes inflammation of the stomach, or gastritis, and has long been proven to cause peptic ulcer disease. Parsonnet said a 1993 study showed that people who took antibiotics had no recurrence of peptic ulcer disease, while people who took a placebo or antacid therapy had nearly 100 percent recurrence of the illness.

Physicians had known that stomach cancer arose from areas of inflammation called chronic gastritis. Using an epidemiologic design, Parsonnet demonstrated that *H. pylori* was not only a strong risk factor for stomach cancer, but it also significantly increased the risk for stomach lymphoma. Other researchers proved this association by using anti-*H. pylori* antibiotics to eliminate lymphoma.

Since then the International Agency for Research on Cancer has classified *H. pylori* as a type 1 carcinogen, but its listing is complicated. *H. pylori* has been linked to many diseases, including diabetes, yet it appears to prevent esophageal cancers, asthma, and maybe even food allergies.

"*H. pylori* is just one bacterium out of the many thousands of bacterial species that live on the human body," Parsonnet said. "I believe we're going to find that most diseases, if not caused by infections, are amplified by the existence of infections."

NIEHS Scientific Director Darryl Zeldin, M.D., presented Parsonnet with the Hans L. Falk plaque, named in honor of the Institute's first scientific director, who made outstanding contributions to environmental health sciences research. (Photo courtesy of Steve McCaw)

You are more microbe than human

Parsonnet said that, according to the Human Microbiome Project, we have 4,000 different microbial species in the gut, 800 in the mouth, 1,300 in supragingival plaque on our teeth, and unknown numbers in parts of the body we once thought were sterile. The total translates into ten times the number of microbial cells as human cells, and 100 times more microbial genes, called the metagenome, than human genes. Astonishingly, that's only counting bacteria.

"When we say microbiome, we're mainly talking about bacteria, but there are viruses, bacteriophages — viruses that live inside bacteria — fungi, and mites," she said. "They're the ones steering the ship, and we know virtually nothing about them."

After a thoroughly engaging seminar, Rogan summed up why Parsonnet was a good choice for this year's Falk lecture.

Infections and the growing problem of obesity

Currently, Parsonnet is studying how early childhood infections affect development, specifically weight gain. The traditional view holds that eating too much, and not burning enough, calories makes people fat, but not all food is absorbed. How little or how much depends on whether a child lives in the developed or developing world. Moving a baby from the developing world to the developed world increases its absorption rates.

Microbiome research in mice has determined that transferring the microbiota from a thin mouse to a fat mouse will make the fat mouse thin and vice versa. This change happens without altering the animal's diet, and suggests there's more to the story of obesity in the United States. Parsonnet believes the answer may relate to Americans dealing with fewer infections. Since infections make the body expend a lot of energy, better hygiene and the disappearance of vaccine-preventable diseases may have removed a natural barrier that kept us from being heavier.

"In the 1960s and 70s, people had rheumatic heart disease, tuberculosis, or chronic diarrhea as children. They weren't as healthy as we are today," Parsonnet said. "Some of this weight gain may be a healthy thing for us, so we should stop fixating on body types that are dated."

"Dr. Parsonnet is a rare combination — clinician, scientist, and educator," Rogan said. "I saw her give a great talk at a meeting several years ago, and I have been trying to get her for the Falk lecture ever since."

Falk family members look forward to the lecture every year. From left to right, Rogan, Parsonnet, Zeldin, Gabrielle Falk, Stephen Falk, J.D., Raymond Falk, Ph.D., Michael Falk, Donald Falk, M.D., and London. (Photo courtesy of Steve McCaw)

Return to Table of Contents

Nano consortium hits stride in middle age

By Eddy Ball

In 2010, NIEHS took a bold step forward, by supporting the NIEHS Centers for Nanotechnology Health Implications Research (NCNHIR) Consortium, bringing together researchers, funded through several grant mechanisms, to accelerate understanding of the health implications and risks associated with engineered nanomaterials (ENMs). Now in its third year, the consortium's eight centers gathered once more at NIEHS Feb. 25-26 for an annual review of its progress toward that goal.

Nadadur opened the third annual meeting of the NCNHIR Consortium with an impressive catalogue of its accomplishments, midway through its five years of operation. His timeline showed that, with consortium data centralized in the CEBS database, the project is on track to meet its 2015 deadline for defining the scientific basis for risk characterization and risk assessment. (Photo courtesy of Steve McCaw)

The meeting began with a welcome by NIEHS Deputy Director Rick Woychik, Ph.D., that included a cautionary assessment of the current understanding of ENMs, which have become ubiquitous in the environment. "The sobering thing is how little we know about the potential deleterious health effects of these materials," he said. "Fortunately, we've made some progress over the past few years…, but there's still a lot of work that needs to be done."

By the time the meeting came to a close, however, participants were talking optimistically about the potential insights that could come, as the enormous amounts of data generated by each of the centers' projects are collected in the Chemical Effects in Biological Systems (CEBS) database, housed at NIEHS. As NIEHS Program Manager Sri Nadadur, Ph.D., explained, "Once we have the data centralized in CEBS, it should be easy to identify the gaps [in our research]."

The program moved quickly as center project representatives presented their updates. Shown above, Imperial College researcher Terry Tetley, Ph.D., center, answered questions as she handed over the podium to colleague Kian Fan Chung, M.D., D.Sc. (Photo courtesy of Steve McCaw)

Looking across models

A major goal of the five-year NCNHIR consortium program, from the beginning, has been to build an integrated, strategic research program — ONE Nano — to increase fundamental understanding of how ENMs interact with living systems, develop predictive models for quantifying ENM exposure and assessing ENM health impacts, and guide the design of next-generation ENMs to minimize adverse health effects.

Using mice, rats, zebrafish, and human cell lines as models, multidisciplinary teams of scientists have tested the toxic effects of as many as 20 different ENMs and how the most common coatings impact the dissolution rate of ENMs in biological systems. Most of the research has focused on lung, the most common route of entry, but several projects have looked beyond the lung to the effects of ENMs on distant organs and the cardiovascular, digestive, and reproductive systems.

Consortium milestones

In Nadadur's update on this ambitious project, he underscored the ways the consortium is shaping discourse about health effects of ENMs. The expansion of nano publications and the increasing visibility of nano research at major meetings are just a few examples of the consortium's influence.

- There have been 28 papers published — 18 of them in 2012, alone — with an additional 18 manuscripts under review and 12 more in preparation.
- Consortium research was highlighted at the 3rd U.S.-China Symposium on Nanobiology and Nanomedicine Dec. 4-7, 2012, in Beijing.
- Members participated in the ASME (founded as the American Society of Mechanical Engineers) 2nd Global Congress on NanoEngineering for Medicine and Biology Feb 4-6, in Boston.
- The Society of Toxicology annual meeting will have six symposium talks and 24 posters on consortium research.
- Consortium investigators (predictive modelers) will be invited to participate at an upcoming meeting of the National Nanotechnology Initiative on risk assessment.
- There are plans to showcase NCNHIR consortium efforts at NANOTOX 2014, the 7th International Nanotoxicology Congress in Turkey.

Along with their independent research projects, eight of the centers and consortium partners collect and share data about a common set of ENMs — four different silver nanoparticles, and multiwalled carbon nanotubes with several different aspect ratios. This work complements work on these same materials by NTP.

Along with exploring potential effects on distant organs, consortium researchers, such as Martin Philbert, Ph.D., of the University of Michigan, and Harvey Clewell, Ph.D., of the Hamner Institutes for Health Sciences, are asking new questions about ENMs. During a discussion on day two of the meeting, Philbert speculated about effects of ENMs in the extracellular space, and whether nanoparticles end up in cells or between cells. As Clewell said in his presentation, "We [also] have to consider the possibility of secondary mechanisms."

The next step

"Part of CEBS is to make sure that all the nano data generated from NIEHS and NTP funding will be made accessible for any modeling efforts that anyone wants to carry out," Nadadur explained. "Each of the centers has three projects — one to look at the interaction of ENMs and biological systems at the cellular level, one at the animal level — and both should interact. Then this data should be used by project three within the centers to see whether we can develop any models to predict hazards associated with exposure."

Nadadur estimated that researchers should be able to submit their data by this summer. "All of this work has led to the generation of quality data, comparable across the centers, that is more valuable for modelers to use," he said.

While the *in vitro* and *in vivo* studies involved hypothesis-driven research, the next phase of the consortium's work will involve synthesis of data for novel meta-analysis. Its progress will be a topic of discussion at the next consortium meeting in September.

During the meeting's poster session, University of Washington postdoctoral research fellow Ryan McMahan, Ph.D., left, described his team's research to North Carolina State University toxicologist James Bonner, Ph.D. (Photo courtesy of Steve McCaw)

The poster session also gave consortium members an opportunity to talk about their accomplishments and future plans. Philbert, left, joined University of California, Los Angeles project director Andre Nel, M.D., Ph.D. (Photo courtesy of Steve McCaw)

RTI International metabolomics center director Susan Summer, Ph.D., left, shared data with University of Michigan toxicologic pathologist Ingrid Bergin, V.M.D. (Photo courtesy of Steve McCaw)

NIEHS Senior Toxicologist Chris Weis, Ph.D., was one of several scientists at the meeting representing Institute research divisions and, in Weis' case, the Office of the Director. (Photo courtesy of Steve McCaw)

NIEHS Outstanding New Environmental Scientist awardee Jared Brown, Ph.D., of East Carolina University, presented data on cellular uptake, clearance, and effects of carbon and silver ENMs in epithelial and endothelial cells. (Photo courtesy of Steve McCaw)

Jennifer Fostel, Ph.D., head of the CEBS team, waited patiently for her turn before the consortium's steering committee. The consortium is looking to centralization of its mass of data, to advance risk science for ENMs, using the combined capabilities of the consortium. (Photo courtesy of Steve McCaw)

Former NIEHS Senior Science Advisor Sally Tinkle, Ph.D., enjoyed a place at the table by virtue of her role on the consortium's advisory committee. Tinkle currently serves as deputy director of the National Nanotechnology Coordination Office of the National Science and Technology Council. (Photo courtesy of Steve McCaw)

A veteran of NIEHS and NTP advisory boards, University of Washington toxicologist Elaine Faustman, Ph.D., went straight to the heart of the matter with her comments. "We know there's a lot of dosimetry data out there," she said. "It's just not in a form that we can easily access." (Photo courtesy of Steve McCaw)

Return to Table of Contents

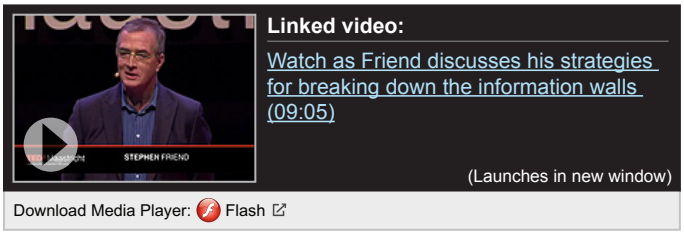
Friend promotes a revolution in biomedical research

By Eddy Ball

Researchers at NIEHS and guests from nearby institutions had an opportunity March 1 to hear from scientist and visionary Stephen Friend, M.D., Ph.D., during a talk hosted by NIEHS and NTP Director Linda Birnbaum, Ph.D. The title of his talk, "Integrating Genomes and Networks to Understand Health and Disease," reflected just how ambitious Friend's plans are, as well as his systems biology approach to discovery.

As he pointed to the sea of stars on his slide, Friend compared what is happening in biomedical research to an early 20th century revolution in astrophysics. In 1911, cosmologist Edwin Hubble was able to show that instead of one galaxy, there were some 100 million galaxies the size of our own, forming a far more complex network than astronomers had previously imagined. (Photo courtesy of Steve McCaw)

With outstanding credentials as a scientist and clinician, Friend is a fitting leader for the mission of transforming how scientific discovery happens, by challenging the traditional competitive culture of science. His model marries big data, social media, and participatory science, in a way that challenges the hierarchy of science and takes a much more data-intensive approach to scientific discovery.



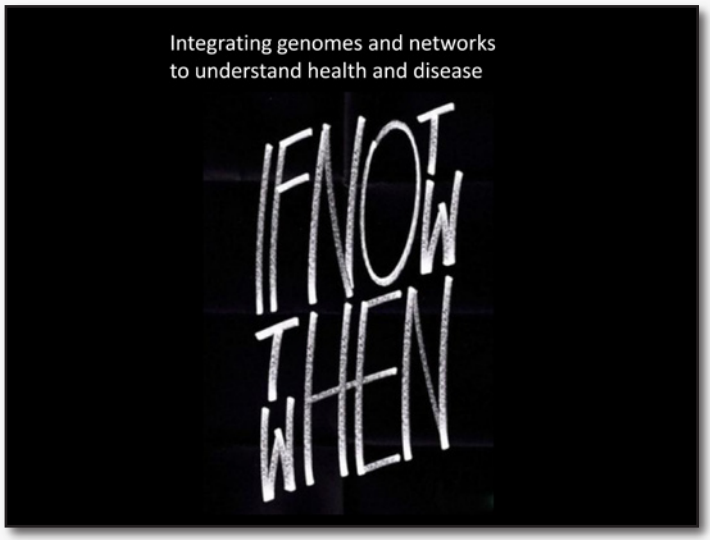
Linked video:

Watch as Friend discusses his strategies for breaking down the information walls (09:05)

(Launches in new window)

Download Media Player: Flash

Friend envisions an open-access scientific commons, where the contributions of patients and citizen scientists may prove to be as valuable as those of tenured scientists at privileged institutions. "We're at the edge of a totally remarkable transition," Friend said of the biomedical revolution at hand. "Things happen when people care and they're passionate and they have energy, not because they have degrees."



Friend opened and closed his presentation with this question, which reinforces the urgency and timeliness of his proposal. (Graphic courtesy of Sage Bionetworks)

Open systems of sharing in a commons

At the heart of Friend's vision is the enormous amount of data that would be available if teams of individual researchers, their institutions, patients, and pharmaceutical companies combined their resources. For the model to succeed, each of these stakeholders needs to modify attitudes toward recognition, ownership of data, patient consent, and intellectual property protection.

Underscoring the complexity of biological systems, Friend pointed to built-in redundancy and overlapping pathways that he said help explain why scientists, looking at the same mechanism, may get different results. "We don't know how to think in those multiple dimensions, and until we learn …, we're going to be puzzled by the answers we get back, in terms of how they don't fit together," he said.

As Friend envisions this new community science, harnessing that volume of data in an unbiased, what he called naive, search for new patterns, could lead to insights for reducing and eliminating disease. "You can look at unknowns," Friend said, "if you have a large enough compendium."

Obstacles and promise

Although Sage Bionetworks, the non-profit Friend co-founded, has made significant progress in securing free cloud computing space and launching an online consent project, there remain important challenges. He admits that giving researchers timely and adequate reward for their work on teams remains problematic. Restrictive consent forms proved to be a barrier for pharmaceutical companies and others who are willing to share data.

However, Friend said, "I think the whole world is waking up to this." Referring to the 2011 Institute of Medicine (IOM) report, "Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease," He explained that the kind of biomedical breakthroughs he envisions ultimately depend on a fundamental change in how researchers perceive information and derive meaning from it.

"What it [the IOM report] basically said is, if we're going to shift from symptom-based to one that takes molecular characterization into account, we've got to build a new taxonomic classification system," said Friend. "To do that, we need an information commons and we need a knowledge network."

In an effort to move this open-access network science forward, Friend and colleagues have conducted high-profile proof-of-principle studies. Borrowing a concept from Star Trek, they also formed a federation to host seed projects.

The first of the federation's challenge projects launched last summer, the Sage Bionetworks - DREAM (Dialogue for Reverse Engineering Assessments and Methods) Breast Cancer Prognosis Challenge, marshaled the diverse talents of 1,700 teams from 40 countries. To Friend's obvious delight, the winner turned out to be a physicist who took an approach he said electrical engineers would take, not one doctors would — an example of the potential of his inclusive model for advancing scientific discovery.

Not surprisingly, the capacity audience included statisticians involved in big-data projects, such as NIEHS lead researcher Dmitri Zaykin, Ph.D., above, and Fred Wright, Ph.D., of the Carolina Center for Genome Sciences at the University of North Carolina at Chapel Hill. (Photo courtesy of Steve McCaw)

NIEHS staff on hand for Friend's talk included, left to right, bioinformatics scientist David Fargo, Ph.D.; senior associate scientist Dmitri Gordenin, Ph.D.; Scientific Director Darryl Zeldin, M.D.; and Senior Advisor Allen Dearry, Ph.D. (Photo courtesy of Steve McCaw)

Among the many NIEHS attendees with varying interests in Friend's project were, left to right, Molecular Genomics Core biologist Stella Sieber and NTP toxicologist Stephanie Smith-Roe, Ph.D. (Photo courtesy of Steve McCaw)

Health Science Administrator Thad Schug, Ph.D., was one of several NIEHS Division of Extramural Research and Training grant administrators who attended the talk. (Photo courtesy of Steve McCaw)

Birnbaum, right, moderated the question-and-answer segment of the presentation. Friend praised NIEHS leadership for its willingness to embrace new ideas, and cited the Tox21 consortium as an example of progressive data-intensive network science. (Photo courtesy of Steve McCaw)

Supporting a new approach to scientific discovery

Friend described five scientific and social developments that are the building blocks for networked science.

- **Data —** It is now possible to generate a massive amount of human 'omics data. "We're now capable of doing data-driven science in a way we weren't ten years ago."
- **Modeling —** Network modeling approaches for diseases are emerging that utilize three or more layers of information. "If you only have two layers of information, you're talking about associations. When you have three and four layers of information, you can begin to build causal and non-causal linkages between components that actually begin to build up and look at relationships."
- **Internet —** Information technology infrastructure and cloud computing capacity now allows a generative, open approach to biomedical problem solving. "Data generated in one place can be truly accessible to everyone."
- **Patient empowerment —** There is growing movement among patients for controlling sensitive information themselves to allow for sharing. "They generate it for free, they're very interested in putting it together, and you're not paying them to do it. We've got to find some way of pulling that data in, because of the depth of it."
- **Gaming —** Open social media allows citizens and experts to use gaming to solve problems, often outperforming the so-called experts with advanced degrees. "When large groups of people get together and work on things, you're tapping into an energy that doesn't cost a lot of money."

Return to Table of Contents

First two substances peer reviewed for listing in new Report on Carcinogens

By Robin Mackar

A panel of experts concurred with the National Toxicology Program's preliminary decision to list 1-bromopropane and cumene as reasonably anticipated human carcinogens, based on sufficient laboratory animal data.

These are the first two chemicals to be peer reviewed as part of a new process for evaluating substances for the 13th Report on Carcinogens (RoC).

In an open meeting that was also webcast, the panel, which met March 21-22, was charged with reviewing the draft documents, referred to as monographs, and voting on whether the scientific evidence presented supports the NTP's listing decisions. The RoC can list substances in one of two categories — known to be human carcinogens or reasonably anticipated to be human carcinogens.

Each RoC monograph is comprised of a cancer evaluation component, which lays out all the information used to make a listing decision, and a substance profile, containing both the NTP's listing recommendation and a summary of the scientific information considered key to reaching that recommendation. The development of the draft monograph is one of the newer additions to the RoC evaluation process.

"We wanted to create a document that clearly illustrates how we came to our conclusions about listing a substance," said NTP Associate Director John Bucher, Ph.D.

The panel appeared to like the draft monographs. "This is about the third time I've served on a peer review committee for the NTP, and I must say you really hit your target in the way you are developing your documents and getting public input," said panel member Wayne Sanderson, Ph.D., of the University of Kentucky.

Lunn provided an overview of the RoC process at the peer review panel meeting. (Photo courtesy of Steve McCaw)

Consultant Stephen Nesnow, Ph.D., right, an organic chemist by training, and a well-known expert on chemical carcinogenesis, offered many thoughtful comments on both the cumene and 1-bromopropane draft monographs. Nesnow was seated next to Bucher. (Photo courtesy of Steve McCaw)

Cumene

Ruth Lunn, Dr.P.H., director of the Office of the Report on Carcinogens (RoC), outlined the process for developing the documents. Next, Mary Wolfe, Ph.D., director of the NTP Office of Liaison Policy and Review, identified scientific issues in the written public comments on the substance, and asked the panel to carefully consider the public comments.

NTP health scientist Gloria Jahnke, D.V.M, gave the presentation on cumene. Cumene is a colorless liquid, primarily used to make other chemicals, including acetone and phenol. It is also found in fossil fuels, such as blended high octane gasoline and kerosene.

Chairperson Anderson, left, consulted with Wolfe about the charge to the panel. (Photo courtesy of Steve McCaw)

The panel spent time discussing whether or not a significant number of persons in the United States were exposed to cumene. Chair Lucy Anderson, Ph.D., summed up the panel conversations by saying the committee thinks that the occupational and environmental exposure data presented qualifies as significant.

The panel voted to concur with NTP to list cumene as a reasonably anticipated human carcinogen. The panel's conclusions were based on tumors found in lung and liver, but, since there was not consensus about the renal tumors, the panel decided to recommend adding renal tumors as supporting evidence for the listing.

1-bromopropane

NTP health scientist Diane Spencer walked the panel through the science of 1-bromopropane, which is a solvent used as a cleaner to degrease electronics and metals, and may be used in some dry cleaning operations. The panel agreed that the chemical is significant to public health.

Lawrence Lash, Ph.D., of the Wayne State University School of Medicine, reviewed his notes, while sharing his comments with fellow board members and NTP staff. (Photo courtesy of Steve McCaw)

Because there were no human studies to consider, Spencer presented the animal data showing the substance caused skin tumors in male rats, large intestine tumors in male and female rats, and lung tumors in female mice.

Reviewer Terry Gordon, Ph.D., of the New York University Langone Medical Center, agreed with the data presented, saying he felt the rodent data were biologically relevant to humans, but remained puzzled by the different gender effects.

Although there were few mechanistic data available, the panel generally agreed with NTP conclusions on the genotoxicity data. They felt the overall evaluation was an effective synthesis of integrating the metabolic, genotoxic, and mechanistic data with the carcinogenicity results.

The panel also discussed the role that immunosuppression may play in tumor development in animals. "Immunosuppression needs to be mentioned and emphasized more in the document," said Paul White, Ph.D., of Health Canada, with concurrence from MaryJane Selgrade, Ph.D., of ICF International.

The panel unanimously voted to list 1-bromopropane as reasonably anticipated to be a human carcinogen, based on the animal studies presented by NTP.

The documents will be revised based on comments, placed on the public website, and shared at a public meeting with the NTP Board of Scientific Counselors.

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

Jahnke walked the panel through the cumene animal literature. (Photo courtesy of Steve McCaw)

Panel member Sanderson had many positive comments to make about the documents and the RoC process. (Photo courtesy of Steve McCaw)

While at NIEHS, Paul White also shared his expertise on chemical mixtures, during a separate talk hosted by NTP earlier in the week. (Photo courtesy of Steve McCaw)

Lunn, left, and Jahnke responded to questions from the panel about the cumene literature. Spencer joined Lunn the next day to present on 1-bromopropane. (Photo courtesy of Steve McCaw)

Peer reviewer Michael Elwell, D.V.M., Ph.D., left, from Covance Laboratories Inc., and Gordon provided comments on the draft documents. (Photo courtesy of Steve McCaw)

Wolfe, left, and Bucher were clearly pleased with the input they received from the public and the panel. (Photo courtesy of Steve McCaw)

Return to Table of Contents

Study uncovers details of allergic response in asthma patients

By Robin Arnette

According to research performed by NIEHS scientists, an enzyme normally produced in the body to help fight inflammation, also suppresses allergic responses in asthma patients. The study, which appeared online Feb. 28 in the American Journal of Respiratory and Critical Care Medicine, may help researchers understand the development and exacerbation of asthma.

The research team found that knocking out the enzyme cyclooxygenase-2 (COX-2) in mice, or treating normal mice with COX-2 inhibitors, led to elevated levels of a special type of helper immune cell. These immune cells, called T helper type 9 (Th9), are associated with asthma.

Hong Li, Ph.D., is a research fellow in the NIEHS Laboratory of Respiratory Biology and first author on the report. He and his colleagues tested three groups of mice — normal mice with functional COX-2 as a control, normal mice that were given COX-2 inhibitors, and mutant mice that lacked the COX-2 gene. They allowed the mice to become allergic to ovalbumin, the main protein in egg whites, by exposing them to the protein. The researchers then measured how many Th9 cells each group made and their levels of COX-2 metabolites.

In addition to his duties as NIEHS Scientific Director, Zeldin also heads the Environmental Cardiopulmonary Disease Group in the Laboratory of Respiratory Biology. (Photo courtesy of Steve McCaw)

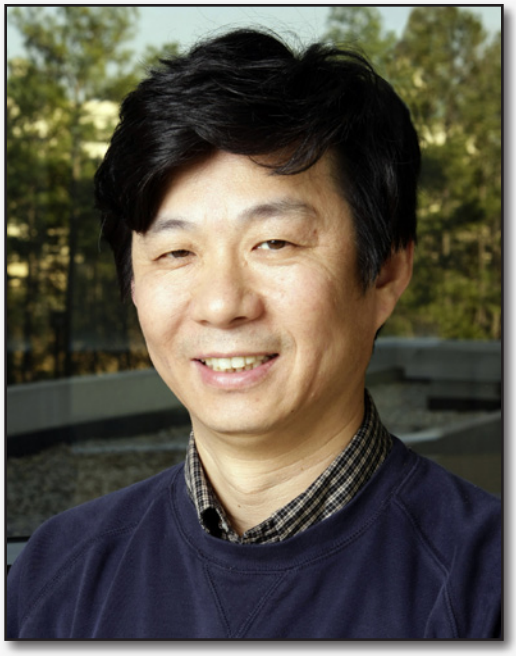
"The control mice had very few Th9 cells, while the COX-2 inhibited mice and the mice without the COX-2 gene made double the number of Th9 cells," Li said. "Our results show that COX-2 is responsible for suppressing Th9 cell formation."

As a reinforcement of their findings, the researchers also tested healthy human adults and asthmatics, and found that the asthma patients had significantly more Th9 cells.

Li explained that although Th9 cells are associated with asthma, they normally help fight infections. This dichotomy arises because Th9 cells secrete a chemical messenger, or cytokine, known as interleukin 9 (IL-9), which increases inflammation in the body and leads to the exacerbation of asthma symptoms.

According to NIEHS Scientific Director Darryl Zeldin, M.D., corresponding author of the study, the research team was able to pinpoint the key players in the asthma COX-2 mechanism.

"We determined that two of the metabolites of COX-2, prostaglandins E2 and D2, suppress Th9 cell generation and function," he said. "Although this information doesn't provide a cure for asthma, we hope to use what we've learned to help asthma sufferers lessen their symptoms in the future."



Li said the research team is currently investigating whether gene differences, also known as polymorphisms, in COX-2 are associated with asthma. (Photo courtesy of Steve McCaw)

Citation: Li H, Edin ML, Bradbury JA, Graves JP, DeGraff LM, Gruzdev A, Cheng J, Dackor RT, Wang PM, Bortner CD, Garantziotis S, Jetten AM, Zeldin DC. 2013. COX-2 inhibits Th9 differentiation during allergic lung inflammation via downregulation of IL-17RB. Am J Respir Crit Care Med; doi:10.1164/rccm.201211-2073OC [Online 28 February 2013].

Return to Table of Contents

Potential new therapy for stopping cardiac fibrosis

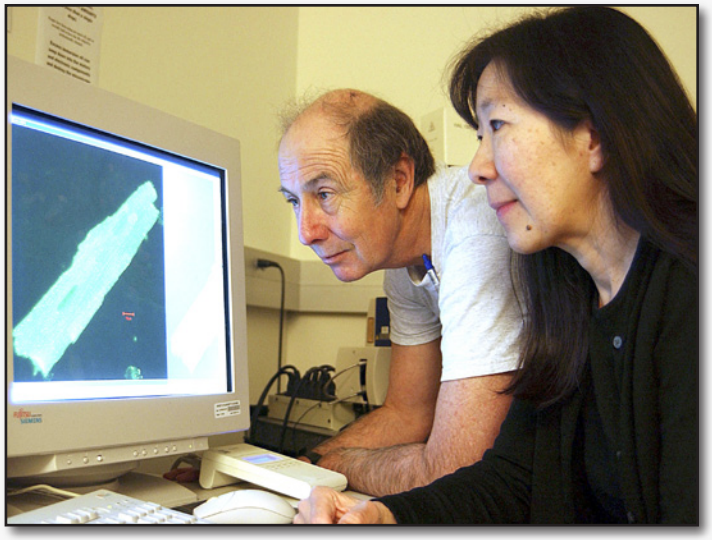
By Carol Kelly

A unique therapy for preventing or reducing harmful cardiac scar tissue, a common development in people following a heart attack, may result from a new finding by NIEHS-supported researchers at the University of California, Davis (UC Davis). Their study shows that blocking an enzyme that promotes inflammation can prevent cardiac fibrosis, scar tissue damage that often leads to heart failure.

"Cardiac fibrosis is a common final pathway for many cardiac diseases and heart failure that has been difficult to treat in the clinic," said Javier López, M.D., a professor at UC Davis specializing in cardiovascular medicine and part of the research team. "This study shines some light onto this pathway and offers perhaps a new therapeutic target that may expand available treatments for these patients in the future."

Inhibiting the enzyme soluble epoxide hydrolase

An 11-scientist team determined the molecular mechanisms underlying the beneficial effects of inhibiting the enzyme soluble epoxide hydrolase (sEH) after a heart attack. The scientists were led by Bruce Hammock, Ph.D., who directs the UC Davis Superfund Research Program, and Nipavan Chiamvimonvat, M.D., a professor of cardiovascular medicine at UC Davis.



Chiamvimonvat, right, and Hammock look over the distribution of an enzyme in a rodent heart muscle cell. (Copyright UC Regents)

In the study, mice receiving sEH inhibitors showed significant decreases in adverse cardiac muscle remodeling, or enlargement, following a heart attack. Their overall cardiac function also improved. Additional tests performed in Hammock's lab indicated significantly reduced levels of inflammatory factors in the mice. The research team hopes to next test the compound on another animal model, as a precursor to human clinical trials.

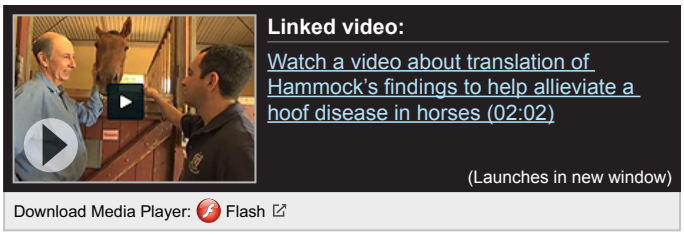
The enzyme sEH typically plays a lead role in tissue healing following an injury. However, this role can become counterproductive after a cardiac event.

Chiamvimonvat explained that sEH exacerbates inflammatory conditions. It also causes the cells that typically link together to provide the foundation for heart tissue to overwork. The outcome is cardiac fibrosis, which results in an abnormal relaxation of the heart after each beat. Undamaged heart muscle is remodeled as it performs double duty, eventually leading to a decline in the heart's pumping action.

Potentially impacting a major public health issue

Heart failure, a condition where the heart cannot pump enough blood to support other organs, affects 5.7 million people in the United States, and costs the nation $34.4 billion in health care services, medications, and lost productivity, according to the Centers for Disease Control and Prevention. About half of the people who have heart failure die within five years of diagnosis.

"This study is the result of a long-term, exciting collaboration between the College of Agricultural and Environmental Sciences and the UC Davis School of Medicine, which has been very productive," said Hammock. "The translational value of our research is significant."



This finding is also the latest in a long line of success in Hammock's research related to sEH inhibitors. Forty years ago, Hammock discovered sEH inhibitors while studying insect development. His previous work with sEH inhibitors led to beneficial discoveries related to controlling blood pressure and treating neuropathic pain associated with diabetes.

Citation: Sirish P, Li N, Liu JY, Lee KS, Hwang SH, Qiu H, Zhao C, Ma SM, Lopez JE, Hammock BD, Chiamvimonvat N. 2013. Unique mechanistic insights into the beneficial effects of soluble epoxide hydrolase inhibitors in the prevention of cardiac fibrosis. Proc Natl Acad Sci U S A; doi:10.1073/pnas.1221972110 [Online 14 March 2013].

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

Return to Table of Contents

Brown SRP scientists partner with ATSDR to discuss nano design

By Sara Mishamandani

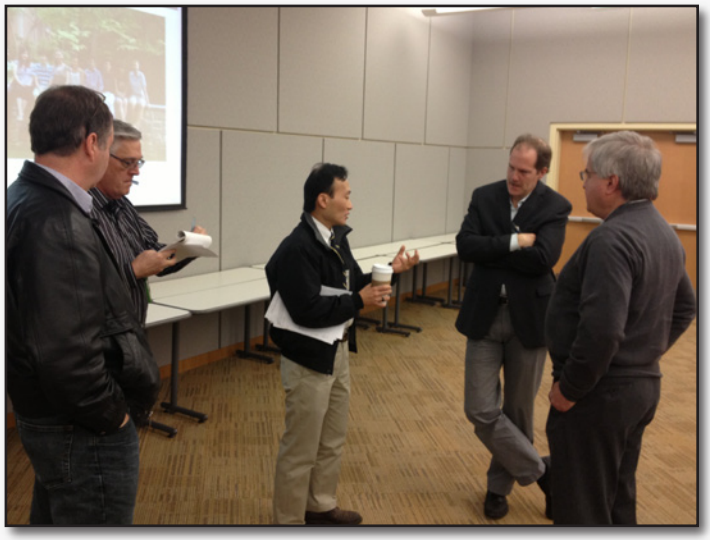
To share their nanomaterial research and foster collaboration with Agency for Toxic Substances and Disease Registry (ATSDR) scientists, Brown University Superfund Research Program (SRP) grantees Robert Hurt, Ph.D., and James Rice, Ph.D., spent Feb. 27 at ATSDR in Atlanta.

Hurt's talk attracted a large audience, from high-level ATSDR managers to staff scientists. (Photo courtesy of Jim Rice)

Nanomaterial design for environmental health

Hurt presented his NIEHS-funded nanomaterial research to an audience of ATSDR and U.S. Environmental Protection Agency (EPA) employees, as an invited speaker in a joint SRP/ATSDR seminar and networking series. Hurt discussed both the applications and implications of nanotechnology for environmental health, one of the themes of the Brown SRP, and the main focus of his project and collaborative work with Brown SRP grantee Agnes Kane, M.D., Ph.D.

"It is interesting to merge the two topics, because one sees the risk-benefit tradeoffs quite clearly," said Hurt. "It also opens up the possibility to design technologies for safety up front, by considering risks at the early stage of development."



After the presentation ended, a long line of researchers stayed behind to continue discussions with Hurt, second from right, on nanomaterial design and safety. (Photo courtesy of Jim Rice)

Because of the potential health implications of nanomaterials, Hurt introduced the need for safety by design, or the reduction or elimination of hazard or exposure through intelligent, science-based synthesis and formulation. Brown scientists are working to understand the materials and molecular basis for nanotoxicity, by creating nanomaterials and testing their biological properties. By better understanding the relationship between nanomaterial structure and activity, the development of general rules for safe nanomaterial design is achievable.

Hurt also described several Brown SRP research projects related to nanomaterial design and safety, including his research to synthesize filled nanosacks made of graphene, which have the potential to allow for controlled release and delivery of therapeutic agents in the body, as well as other biomedical applications.

After his talk, Hurt, left, also chatted with ATSDR Director Christopher Portier, Ph.D. (Photo courtesy of Jim Rice)

Building partnerships and moving forward

Rice, the state agencies liaison in the Brown SRP Research Translation Core, joined in for a networking lunch and discussion session with ATSDR staff and some EPA employees. Rice and Hurt delved into their research ideas, answered general questions about their work, and learned about current research needs from ATSDR staff.

"Based on the feedback by ATSDR staff, the visit assured us that what we are doing at Brown SRP is valuable and relevant," said Rice. "ATSDR and EPA employees also gave us some ideas that will help us formulate new research moving forward."

Rice emphasized that the visit is starting conversation with other agencies and making it known that Brown SRP researchers are available as a resource. He also provided insights into ways to translate nanomaterial research effectively with ATSDR staff.

"It was a very informative visit for me, and my first time at ATSDR," said Hurt. "It was also interesting to hear that the ATDSR is beginning to think about its role in the nanotechnology field."

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

Return to Table of Contents

UNC studies link viral infection response to smoking and nutrition

By Richard Sloane

In addition to the long-term harmful effects of smoking, recent findings suggest that exposure to tobacco smoke may also affect how otherwise healthy people respond to flu infection.

According to NIEHS grantee Ilona Jaspers, Ph.D., who spoke March 8 at Duke University on "Inhaled pollutants and host defense: studies from right under your nose," the effects are the result of oxidant-driven gene expression changes that directly inhibit antiviral pathways in human respiratory epithelium infected with influenza virus.

Jaspers and her team at the University of North Carolina (UNC) at Chapel Hill Center for Environmental Medicine, Asthma, and Lung Biology aren't just looking at the negative impact of tobacco smoke exposure. They're also conducting research on an antioxidant micronutrient found in cruciferous vegetables, such as

broccoli and cauliflower (see text box), that may improve host response and lessen the severity of effects from flu infection, which makes thousands of Americans ill each year and can even result in death for people with compromised immune systems.

Using exposure chambers available in the U.S. Environmental Protection Agency Human Studies Facility at UNC, Jaspers also studies how ambient air pollutants, such as ozone and diesel exhaust, modify innate host defense responses in the context of viral infections. (Photo courtesy of Steve McCaw)

Flu's portal of entry — the nose

Jaspers' studies focused on nasal epithelial cells, since they are the primary targets of respiratory viruses. She explained that in order to study the defense responses, her team used two experimental models. The *in vitro* model uses differentiated human airway epithelial cells, while the *in vivo* model involved an inoculation technique, in human volunteers, with the live attenuated influenza virus (LAIV) vaccine.

LAIV is designed to replicate best in the nasal cavity, which is easy to sample reliably and repeatedly, Jaspers explained. It's also the predominant target for LAIV and offers a very safe way to study influenza infection *in vivo*. The team collected samples by nasal lavage with a saline solution, a simple non-invasive procedure for nasal flushing similar to using a neti pot, from three groups of subjects — smokers, non-smokers, and people who don't smoke but are exposed to second-hand smoke at home or at work.

Jaspers' presentation was part of the Duke University Integrated Toxicology and Environmental Health Program Seminar Series. (Photo courtesy of Steve McCaw)

The samples were analyzed using flow cytometry and various molecular techniques, to determine markers of inflammation. The team found differences in indicators of inflammation. "Nasal epithelial cell populations somehow seemed to lose their ability to effectively communicate with their neighboring cells in smoke-exposed subjects," Jaspers said.

LAIV replication was higher in both smokers and those exposed to second-hand smoke than in non-smokers, indicating that the body's natural immunity to the virus was suppressed in both passive and active smokers. Smokers also displayed response suppression in dendritic, natural killer, and T cells, which are all critically important players in human immune response.

Gene expression changes

According to Jaspers, nasal viral exposure normally induces the production of an antiviral mediator in the nasal epithelium called interferon, an important component of the body's immune system that limits the ability of a virus to self-replicate. In the nasal epithelium of smokers, mechanisms mediating the production of interferon appear to be blunted.

This effect appears to be, at least partially, linked to changes in the methylation of genes, an epigenetic effect of exposure to smoke. Methylation of genes takes place when a methyl group links to a DNA molecule, which can result in silencing of that gene. Jaspers said that, based on previous studies conducted at Boston University, with smoking cessation, total gene recovery or reversibility of damage from smoke exposure is possible for some genes. For others, it may be semireversible and, in some cases, not reversible at all.

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

Exploring secondary prevention

Tobacco smoke is a strong oxidant, and the optimal way to protect people from its effects is to avoid exposure in the first place. But individuals won't or can't always quit smoking or avoid exposure to second-hand smoke.

What Jaspers is now interested in exploring is whether nutritional antioxidants can diminish the harmful effects of tobacco smoke on the nasal epithelium and improve host response to influenza infection. To find out, she is experimenting with a micronutrient called sulforaphane that is found in cruciferous vegetables. All cruciferous vegetables contain sulforaphane, but it is particularly abundant in broccoli.

As Jaspers explained, laboratory studies and NIEHS-funded clinical studies in China have shown that higher intake of sulforaphane may aid in detoxification of cancer-causing contaminants. So Jaspers' team prepared what they call brocco shakes, broccoli sprouts blended with water, for volunteers to consume three days in a row. Controls drank a placebo drink containing shakes made from other sprouts.

At the end of the three days, Jaspers' team collected and analyzed nasal lavage samples from the volunteers. Those who consumed the brocco shakes demonstrated higher antioxidant gene expression patterns than the control group. Jaspers said the results are promising and more studies are forthcoming.

Return to Table of Contents

Researchers offer recommendations for BPA study design

By Melissa Kerr

There is growing uncertainty among the public about whether or not people should be concerned about the health effects of exposure to bisphenol A (BPA). While NIEHS Comparative Medicine Branch microbiologist Julius Thigpen, Ph.D., and colleagues did not try to answer this burning question in their latest work, they do propose a way toward a clearer understanding of the true effects of BPA and other endocrine-disrupting compounds (EDCs) from low-dose exposures.

In an overview of the literature published in the March issue of the Journal of the American Association for Laboratory Animal Science, Thigpen and colleagues find that results from low-dose BPA studies are inconsistent, and concludes that some of the discrepancies are likely due to differences in study designs.

Call for consistency

Thigpen and colleagues argue that when scientists design studies of EDCs, they should take into account the kind of diet used, as well as the choice of bedding. The researchers conducted one review of 69 publications from 1997 to 2004, and a second review of 103 publications from 2005 to 2010. One of the foremost inconsistencies they found was in the identification of the diet and its phytoestrogen content.

According to Thigpen, diet is an important issue, because most rodent diets contain natural phytoestrogens that have been shown to cause estrogenic effects, which may affect the activity of EDCs. Of the 172 studies reviewed, only 37 percent adequately reported what kind of diet was used, and only 20 percent reported using a phytoestrogen-reduced diet.

Another basic aspect of rodent care that may cause inconsistent findings is the bedding used in cages. Corncob bedding frequently contains a fungus that produces an estrogenic mycotoxin called zearalenone, which has been shown to have greater estrogenic potency than BPA, for some hormonal endpoints.

"We didn't attempt to answer the BPA question," Thigpen said of the group's new paper. "We want this to be a positive way for scientists to move forward with more clarity." (Photo courtesy of Steve McCaw)

Back to basics

Thigpen and colleagues believe their overview will help underscore the importance of removing as many unnecessary variables in EDC studies as possible. "We are trying to reduce the background noise, so that we can better see the EDC signal," explained NTP biostatistician Grace Kissling, Ph.D., a co-author on the study.

The overview stresses that when conducting studies of BPA or other EDCs, scientists should choose a low phytoestrogen or phytoestrogen-free diet. The group also recommends alternatives to corncob bedding, in an attempt to remove a source of yet another estrogenic compound that may confound study results. In an additional recommendation they recognize as potentially controversial, the researchers propose that when the results are to be used to provide data for human risk assessments, researchers should expose animals to BPA by the oral route, rather than subcutaneously, since ingestion is the most likely route for human exposure.

"I think that if investigators follow these recommendations, the quality of research will improve," Thigpen concluded.

Citation: Thigpen JE, Setchell K, Kissling GE, Locklear J, Caviness GF, Whiteside T, Belcher SM, Brown NM, Collins BJ, Lih FB, Tomer KB, Padilla-Banks E, Camacho L, Adsit FG, Grant M. 2013. The Estrogenic Content of Rodent Diets, Bedding, Cages, and Water Bottles and Its Effect on Bisphenol A Studies. J Am Assoc Lab Anim Sci 52(2):130-141.

(Melissa Kerr studies chemistry at North Carolina Central University, and is an intern in the NIEHS Office of Communications and Public Liaison.)

Return to Table of Contents

NTP hosts review of endocrine disruptor screening

By Eddy Ball

To help advance the U.S. Environmental Protection Agency (EPA) Endocrine Disruptor Screening Program (EDSP), NTP and NIEHS hosted a Society of Toxicologic Pathology (STP) regional working meeting March 21 on pathology endpoints. The meeting attracted some 75 attendees, including NTP scientists Darlene Dixon, D.V.M., Ph.D., and Paul Foster, Ph.D., who participated in breakout sessions, following presentations by representatives of regulatory agencies, sponsors, and contract research organizations currently involved in these studies.

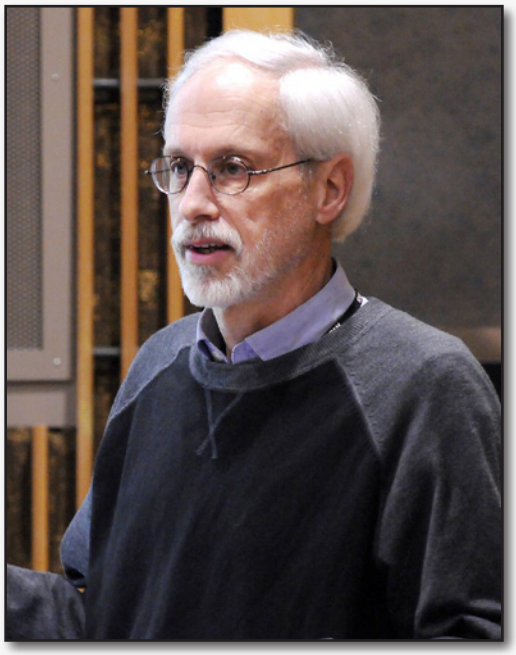
Dixon introduced Bucher, who was the first speaker at the meeting. Dixon was a member of the meeting organizing committee and co-leader of the Female Reproductive Assay Breakout Group. (Photo courtesy of Steve McCaw)

The attendees conducted a critical evaluation of EPA guidelines for conducting pathology assays of pubertal developmental and thyroid function in intact juvenile/prepubertal rats, which are part of the 890 series of endocrine disruptor assays, and developed recommendations that will be made available in 6 to 12 months as a best practices publication in the society's journal, Toxicologic Pathology.

The pubertal developmental and thyroid function assay guidelines are part of a comprehensive program, launched by congressional mandate in 1996, to evaluate the effects of endocrine disrupting compounds (EDCs) in humans and animals, using validated testing, much of it developed specifically for the program (see text box).

Part of the evolution to predictive toxicology

NTP Associate Director John Bucher, Ph.D., welcomed workshop attendees with an overview of NTP that helped place the animal testing, being considered in the workshop, within the context of the emerging paradigm of predictive toxicology under development by the Tox21 consortium. Bucher spoke to NTP's major focus on EDC exposure during development, and long-term health effects. Bucher pointed to five-generation estrogenic compound studies, and the bisphenol A clarity study underway in conjunction with the National Center for Toxicological Research (see story).



Bucher underscored NTP interests in developing new methods for studying EDCs, identifying new ways of integrating information about chemical toxicity, and advancing adequate and accurate pathology. (Photo courtesy of Steve McCaw)

Although the main thrust of predictive toxicology is expanding *in vitro* high-throughput screening, Bucher and the speaker who followed him, EPA lead scientist Doug Wolf, D.V.M., Ph.D., emphasized that streamlined rodent pathology studies, based on the principles of good laboratory practices, continue to be critical in decision-making. They agreed, as well, that regulatory agencies need to move forward using best practices achieved through the consensus of expert pathologists.

The devil in the details

STP Education Committee consultant Kevin Keane D.V.M., Ph.D., served as facilitator for the meeting. As he emphasized, "This is an open meeting that is not on behalf of any one stakeholder in these assays, but rather is intended to be a collegial discussion of the science at hand." On a humorous note, Keane described the meeting's goal — "To reach a consensus, as much as you can get a group of pathologists to reach a consensus."

Despite Keane's tongue-in-cheek caveat, and the number of practical matters the group could not agree on, the group reached consensus on many important points, including the value of including the male mammary gland and female vagina as organs to study, as well as the use of humane practices for anesthetizing animals.

In remarks echoed by several of the speakers, Karen Regan, D.V.M., of Regan Path/Tox Services, noted there is also a pressing need for interpathology consistency, standardized methodology, and objectivity. "You don't want to overanalyze these things," she said. "Just describe what you see and interpret later."

In their assessments of the Tier 1 screening, which examines very young animals after 20 to 30 days of exposure to a chemical beginning about three weeks after birth, several speakers pointed to the need for developmental touchstones. "You need to know the normal at this age of animals," said Dianne Creasy, Ph.D., of Huntingdon Life Sciences. "The system needs to be considered as a whole, when you're looking for endocrine disruption."

Because streamlined rodent assays are uncharted territory for many pathologists, presenters and discussants agreed that a number of technical issues will need more discussion, consideration, and specific guidance. As a case in point, in her report on thyroid endpoints, Catherine Picut, V.M.D., J.D., of WIL Research, honed in on one major consideration, as she described the direction in the EPA guidelines to pick a representative area of tissue to describe.

"What does that mean?" she asked attendees. Tellingly, no one seemed to have a ready answer.

After a slow start, EDSP gains momentum

Following careful reviews by experts, in 2009, EPA announced the initial list of chemicals to be screened for their potential effects on the endocrine system, or Tier I testing, and issued requests for data. Testing will eventually be expanded to cover all pesticide chemicals, as well as substances that may occur in sources of drinking water to which a substantial population may be exposed. EDSP involves a battery of *in vivo* and *in vitro* assays of endocrine endpoints in amphibians, fish, rats, and humans.

Through Tier 1 screening, the program hopes to identify chemicals that have the potential to interact with the endocrine system. Tier 2 testing will determine the endocrine-related effects caused by each chemical, and obtain information about effects at various doses.

Endocrine disruptor screening is currently proceeding on three fronts — developing and validating Tier 2 tests; selecting chemicals for screening and testing; and implementing the policies and procedures the agency will use to require screening.

Keane urged attendees to pay attention to the very practical details involved in evaluating a long list of endpoints. Pointing to follicles in the ovary as an example, he asked, "Do you count this?" (Photo courtesy of Steve McCaw)

Wolf explained that the EDSP mandate arose from food quality protection and safe drinking water legislation, and concerns about estrogenic activity in humans. The program expanded later to include wildlife, androgen and thyroid hormone disruption, and agonistic and antagonistic effects. (Photo courtesy of Steve McCaw)

In her review of male screening, Creasy was critical of several of guidelines that called for examining just one testis and epididymis. "I don't know why," she said. "This is so bizarre." The group agreed that, at the least, tissue selected for pathology should come from the same side of the animal. (Photo courtesy of Steve McCaw)

Foster, center right, echoed calls for a better understanding of young animals. "You have a much bigger range of normal," he said. "They are immature. The system isn't running yet." (Photo courtesy of Steve McCaw)

Although he wasn't part of the working group, pathologist Gordon Flake, M.D., was one of several NTP scientists who were on hand for the morning talks, which drew a capacity audience to Rodbell auditorium. (Photo courtesy of Steve McCaw)

As an aside during his report on the Male Reproductive Assay Breakout Group, co-leader George Parker, D.V.M., Ph.D., of WIL Research, struck at the heart of the matter. "Our collective procedures are somewhat haphazard," he said. "There really is some room for science here." (Photo courtesy of Steve McCaw)

At the close of their long day of deliberation, most of the participants gathered on the patio outside the Rall building. (Photo courtesy of Steve McCaw)

Return to Table of Contents

Moving toward a new framework for chemical risk assessment

By Kristen Ryan

Russell Thomas, Ph.D., proposed a practical, data-driven framework that can provide a near-term solution for making economical, efficient, and health-protective decisions on chemicals during a presentation March 15 at NIEHS.

Thomas, who is director of the Institute for Chemical Safety Sciences at The Hamner Institutes for Health Sciences, summarized the movement towards modernized toxicity testing for chemical risk assessment over the past decade, and the difficulties of transitioning the vision proposed in 2007 by the National Research Council (NRC) report on "Toxicity Testing in the 21st Century: A Vision and a Strategy" into reality.

Hosted by NIEHS Program Administrator David Balshaw, Ph.D., the presentation set the stage for what Thomas described as an initial application of 21st century technology to toxicology and risk assessment.

Thomas' presentation drew a capacity audience that included many NTP scientists, along with others from throughout the institute, interested in data-driven research and toxicology. (Photo courtesy of Steve McCaw).

"It's not the ideal solution," he conceded. "In an ideal world, we will be able to take pathway-based approaches to predict toxicity [using *in vitro* assays only], but let's be realistic, that's a couple of decades away. This represents a near term strategy for how to use these approaches, while we begin to figure out how to effectively make those predictions."

Putting new technologies to the test

During his eight years with Hamner, Thomas' research interests have ranged from cancer biology to applied studies in toxicology and chemical risk assessment, with a special emphasis on the development and application of genomic technologies and bioinformatic tools. In his lecture, Thomas focused on evaluating the utility of both high-throughput *in vitro* assays and *in vivo* transcriptomic studies in the three main areas of chemical risk assessment — hazard identification, dose response assessment, and exposure assessment. The studies led him to these conclusions:

- **Hazard identification** — *In vivo* hazard cannot be accurately predicted with the current high-throughput *in vitro* screening data. However, the data can still be used to both separate chemicals based on their relative selectivity in interacting with biological targets, such as nuclear receptors, kinases, and G-protein-coupled receptors, as well as identify the concentration at which these interactions occur.

- **Dose response assessment** — For those chemicals that interact selectively with specific biological targets, dose response assessment can be performed in a mode-of-action context. For those chemicals that interact non-selectively, dose response assessment can be performed using either high-throughput *in vitro* assays or short-term *in vivo* transcriptomic studies, to identify the dose that causes significant biological perturbation.

- **Exposure assessment** — Understanding exposure provides an important context to the dose-response behavior and can be applied to both *in vitro* high-throughput screening data and *in vivo* transcriptomic data.

Thomas concluded his lecture with a tiered approach (see graphic) for utilizing the available data to make decisions in the near future, by relating the level of chemical exposure and the dose of the toxic effect. The tiered approach focuses on the prioritization of chemicals for standard toxicity testing, saving time and money.

Audience response to a new framework for toxicity testing and risk assessment

Among the audience were NTP toxicologists Scott Auerbach, Ph.D., and Chad Blystone, Ph.D. Auerbach responded to Thomas' presentation by saying, "I think the approach that Dr. Thomas is proposing is a practical and efficient solution to challenges we face in relation to untested chemical space."

Landmark report advances predictive toxicology

"Toxicity Testing in the 21 Century: A Vision and a Strategy" addressed the growing backlog of chemicals on the market that have not received adequate toxicology testing. The number of these chemicals is estimated to exceed 80,000.

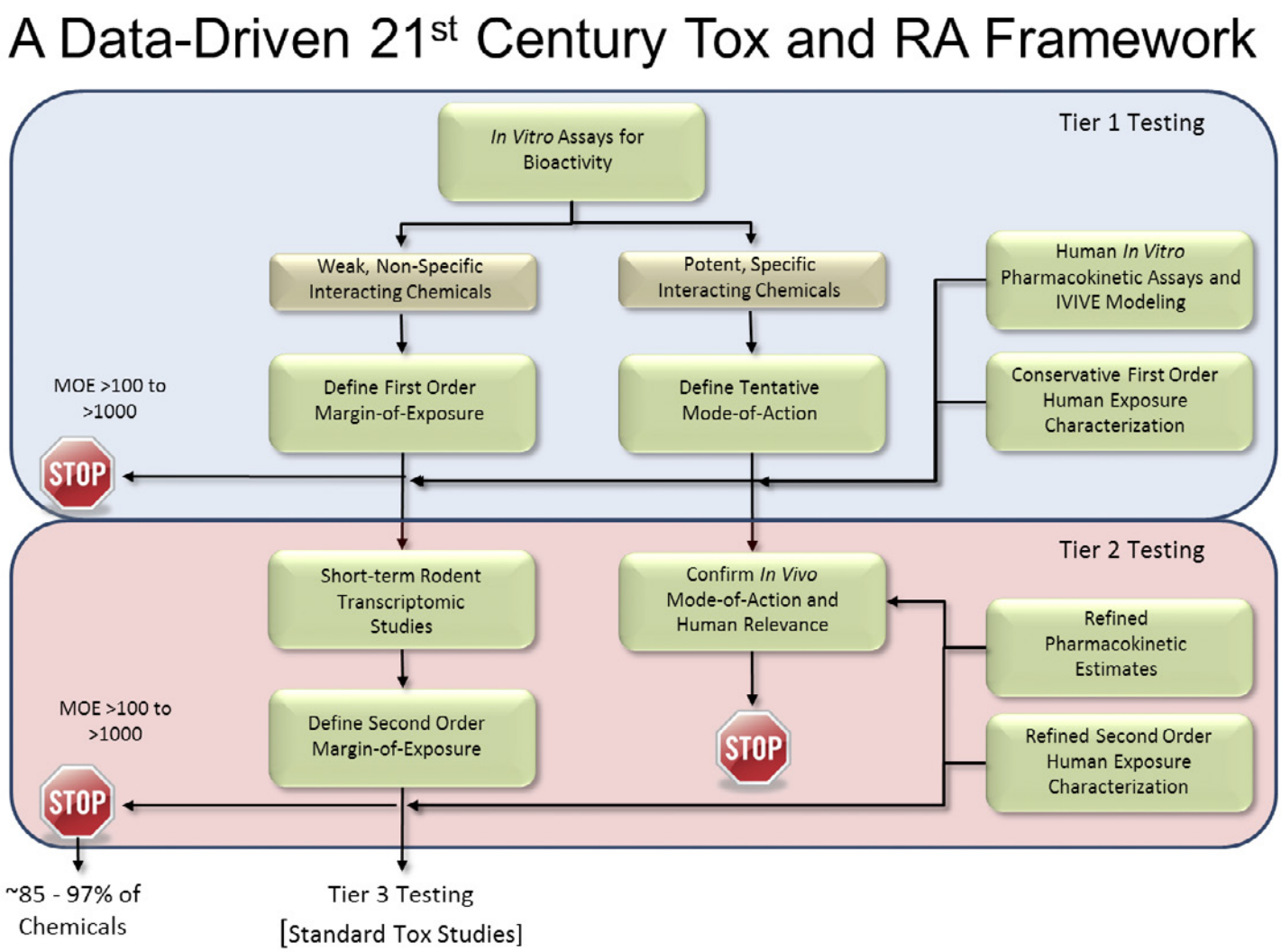
The report proposed development of an *in vitro* high-throughput screening program for identifying chemicals of concern through perturbation of biological or toxicity pathways. The report also helped to support creation of the Tox21 consortium, involving NTP, the NIH Chemical Genomics Center, U.S. Environmental Protection Agency, and U.S. Food and Drug Administration, the consortium's newest member.

In 2012, the consortium began testing 10,000 compounds for potential toxicity. The compounds cover a wide variety of classifications, and include consumer products, food additives, chemicals found in industrial processes, and human and veterinary drugs. Consortium members are acquiring new databases and sharing their existing resources in an ongoing effort to marshal as much information as possible about chemicals and mixtures now in use.

"While the approach does not necessarily identify specific hazards, it does tackle the issue of safety," Auerbach continued. "However, it should be noted that if we are to effectively employ Dr. Thomas's approach, it will be necessary to generate significantly more exposure data."

Blystone concurred by noting, "Dr. Thomas gave a judicious assessment of where high-throughput assays are and are not useful, and provided an interesting path forward to address the issue of lack of toxicity data for many chemicals that the public is potentially exposed to."

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



Thomas estimates that high-throughput screening, combined with short-term rodent transcriptomic studies, may rule out the need for expensive, long-term rodent studies for 85 to 97 percent of inadequately characterized chemicals. (Graphic courtesy of Rusty Thomas)

Return to Table of Contents

This month in EHP

This month's feature stories in Environmental Health Perspectives (EHP) explore questions surrounding human risk for Lyme disease and the safety of food additives.

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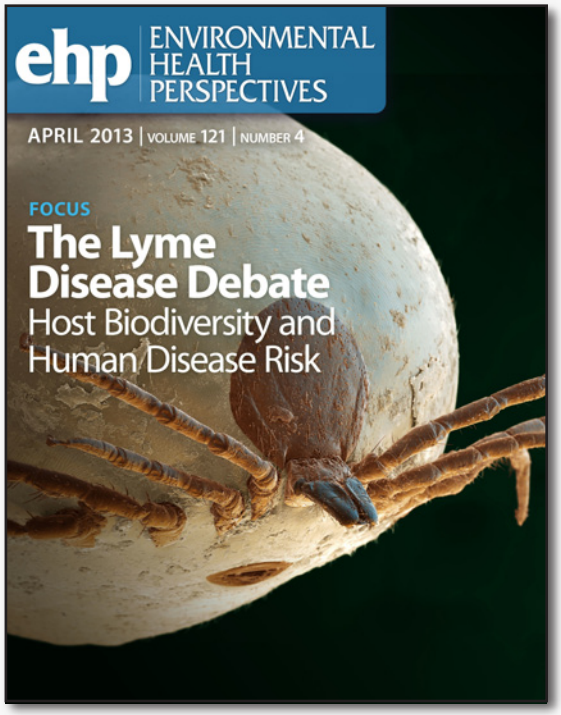
The Lyme Disease Debate: Host Biodiversity and Human Disease Risk

Thirty years after its discovery in the northeastern United States, Lyme disease is the most common vector borne infection in North America. The causative agent, the spirochete Borrelia burgdorferi (Bb), was first isolated from ticks collected in the woodlands of New York. Today, the ecology of Bb is the subject of both intense study and intense scientific debate. Some researchers think protecting large tracts of forest habitat will ultimately reduce the risk of human infection. Others believe the relationship between host biodiversity and human disease risk is not so clear cut.



Food Additives: A Primer

Food additives include all the substances present in a food, from the basic ingredients to those added unintentionally through processing, storage, and packaging. Under current U.S. law, companies can use food additives without U.S. Food and Drug Administration (FDA) premarket approval, as long as the additive is what the agency considers to be generally recognized as safe, or GRAS. This article explores what's involved in earning a GRAS designation from the FDA.

Featured research and related news articles this month include:

- **Managing the Health Effects of Temperature in Response to Climate Change: Challenges Ahead** — Climate Change Adaptation: Weighing Strategies for Heat-Related Health Challenges
- **Prenatal and Postnatal Bisphenol A Exposure and Body Mass Index in Childhood in the CHAMACOS (Center for the Health Assessment of Mothers and Children of Salinas) Cohort** — Unclear Relationship: Prenatal but Not Concurrent Bisphenol A Exposure Linked to Lower Weight and Less Fat
- **Gestational Diabetes and Preeclampsia in Association With Air Pollution at Levels Below Current Air Quality Guidelines** — When Blood Meets Nitrogen Oxides: Pregnancy Complications and Air Pollution Exposure
- **Environmental and Occupational Interventions for Primary Prevention of Cancer: A Cross-Sectorial Policy Framework** — Toward Primary Prevention of Cancer: The Case for a Global Strategy to Limit Avoidable Exposures

Return to Table of Contents

Distinguished Lecture Series talks to explore calcium signaling

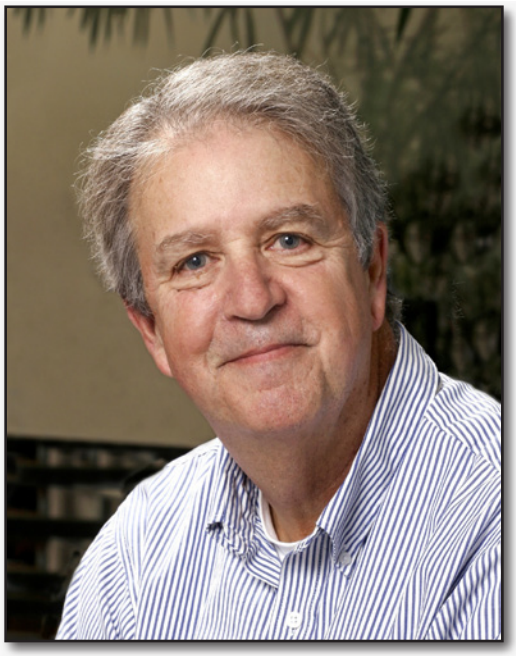
By Sonika Patial

In April, the NIEHS Distinguished Lecture Series will highlight calcium signaling with two talks hosted by lead researcher James Putney, Ph.D., head of the NIEHS Calcium Regulation Group. Both talks will take place from 11:00 a.m. to 12:00 p.m. in Rodbell Auditorium.

Michael Cahalan, Ph.D., will present the first talk April 9 titled "Cracking CRAC — the Calcium Release-activated Calcium Channel of the Immune System." In the second talk April 30, Katsuhiko Mikoshiba, M.D., Ph.D., will explore "Role of IP3 [Inositol 1,4,5-trisphosphate] Receptor Signaling in Development, Cell Function, and Diseases" in the 2013 Dr. Martin Rodbell Lecture.

According to Putney, sometimes calcium signals come from inside the cells and sometimes across the plasma membrane. "Cahalan is highly regarded for discovering very new and unusual types of calcium channels in the plasma membrane that are specifically very important in the immune system," explained Putney. Mikoshiba discovered the most widely expressed interior calcium channels in the endoplasmic reticulum that release calcium."

Both speakers have been honored at the highest levels for their accomplishments. Among other honors, Cahalan is a member and Mikoshiba is a foreign associate of the National Academy of Sciences.

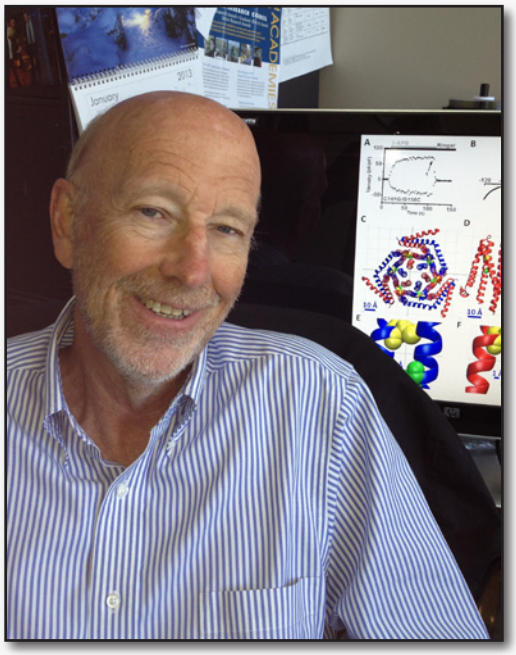


Putney described Cahalan and Mikoshiba as giants in the field of calcium regulation. Both have made seminal discoveries that have advanced understanding of cellular signaling. (Photo courtesy of Steve McCaw)

Giants in the field of calcium signaling

Cahalan is a renowned researcher and professor at the University of California, Irvine (UCI), who is known for his contributions in the area of ion channels and calcium signaling in T lymphocytes. He completed his graduate studies at the University of Washington and a postdoctoral fellowship at the University of Pennsylvania, before joining UCI in 1977,where he has held various positions. Cahalan is currently a distinguished professor and chair of the UCI Department of Physiology and Biophysics.

Much of Cahalan's work is focused on investigating the immune responses at the single cell level, using approaches such as patch clamp to characterize ion channels, and a variety of imaging techniques to monitor motility, cellular interactions, calcium signaling, and gene expression. Cahalan is also highly regarded for his discoveries of the STIM and Orai proteins and their role in store-operated calcium channels.



Cahalan is highly regarded for his discovery of calcium channels in the plasma membrane. (Photo courtesy of Michael Cahalan)

Mikoshiba is senior team leader of the Laboratory of Developmental Neurobiology at RIKEN Brain Science Institute in Japan. He earned his M.D. in 1969 and a Ph.D. in 1971, before becoming a faculty member at the Keio University School of Medicine. Mikoshiba has authored a number of publications, has served as an editorial board member for more than 20 journals, and is a recipient of several highly distinguished honors and awards.

Mikoshiba discovered calcium channels expressed on the endoplasmic reticulum inside the cell. (Photo courtesy of Katsuhiko Mikoshiba)

Mikoshiba's lab studies IP3 and calcium signaling specifically in brain and brain cells. Mikoshiba discovered and cloned IP3 receptor as a calcium channel in the endoplasmic reticulum in early 1990's and, since then, has demonstrated that IP3 receptor plays a highly crucial role in various physiological phenomenon, such as dorso-ventral axis formation in early development, synaptic plasticity, dendrite formation in neurons, fertilization, and endocrine secretion.

The Rodbell Lecture, now in its 15th year, is one of two named talks in the annual NIEHS Distinguished Lecture Series. It honors former NIEHS Scientific Director and Nobel Laureate Martin Rodbell, Ph.D., who presented the first talk in the series shortly before his death in 1998. Rodbell shared the 1994 Nobel Prize in Physiology or Medicine with Alfred Gilman, Ph.D., for the discovery of G-proteins, signal transducers that transmit and modulate signals in cells to control fundamental life processes.

(Sonika Patial, D.V.M., Ph.D., is a fellow in the NIEHS Laboratory of Signal Transduction.)

Return to Table of Contents

Extramural papers of the month

By Nancy Lamontagne

- Contaminated diet contributes to phthalate and bispenol A exposure
- PBDEs may increase risk for Parkinson's disease
- Father's obesity could have epigenetic effects
- SOD1 can repress respiration

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

Contaminated diet contributes to phthalate and bispenol A exposure

An NIEHS-funded researcher and colleagues report that an intervention designed to minimize exposure to bisphenol A (BPA) and phthalates actually led to increases in phthalate concentrations. The study found that people may be exposed to BPA and phthalates in their diets, even when they eat organic food that is prepared, cooked, and stored in non-plastic containers.

The researchers conducted a randomized trial with 10 families. Half of the families receiving a catered diet of local, fresh organic food that was not prepared, cooked, or stored in plastic containers. The other families received written recommendations to reduce phthalate and BPA exposures.

The people who received the meal replacement showed an unexpected increase in urinary di(2-ethylhexyl) phthalate (DEHP) metabolite concentrations, rising from a median of 283.7 nanomoles per gram at baseline to 7,027.5 nanomoles per gram during the intervention ($P<0.0001$). The families who received the written material had no significant changes in phthalate concentrations during this time period. The investigators also saw a statistically significant increase in total BPA concentration between baseline and intervention periods for the families receiving meal replacements, but not in the other families. To identify the source of the exposure, they tested the food ingredients used in the meal replacements and found DEHP concentrations of 21,400 nanograms per gram in ground coriander and 673 nanograms per gram in milk.

The researchers conclude that without regulation to reduce phthalate and BPA concentrations in food production, it may be difficult to develop effective and feasible interventions for the general population.

Citation: Sathyanarayana S, Alcedo G, Saelens BE, Zhou C, Dills RL, Yu J, Lanphear B. 2013. Unexpected results in a randomized dietary trial to reduce phthalate and bisphenol A exposures. J Expo Sci Environ Epidemiol; doi: 10.1038/jes.2013.9 [Online 27 February 2013].

Return to Table of Contents

PBDEs may increase risk for Parkinson's disease

Findings from an NIEHS-funded study point to polybrominated diphenyl ethers (PBDEs) as a possible risk factor for Parkinson's disease and other neurodegenerative diseases.

PBDEs are used as flame retardants and are chemically similar to PCBs, which studies have suggested can increase risk for Parkinson's disease. To see if PBDEs are also neurotoxic, the researchers evaluated the *in vivo* and *in vitro* effects of PBDE mixture DE-71. Previous research showed that vesicular monoamine transporter 2 (VMAT2) mediates dopamine neuron vulnerability and can be inhibited by PBDEs. Thus, they were particularly interested in studying how deficits in VMAT2 expression and function might influence the neurotoxicity of DE-71.

The investigators found that DE-71 caused cell death in a dopamine-secreting cell line and also lowered the number of dopamine-secreting neurons isolated from mice that expressed normal amounts of VMAT2, as well as from mice that expressed approximately 5 percent of normal VMAT2 levels. Mice exposed to DE-71 had significant deposits of PBDE congeners in their brains, reductions in locomotor activity, and less dopamine in the area of the brain associated with Parkinson's disease. These changes were worse in animals deficient in VMAT2. The researchers conclude that their findings warrant additional laboratory and epidemiological research on PBDEs as a potential risk factor for Parkinson's disease and other neurological disorders.

Citation: Bradner JM, Suragh TA, Wilson WW, Lazo CR, Stout KA, Kim HM, Wang MZ, Walker DI, Pennell KD, Richardson JR, Miller GW, Caudle WM. 2013. Exposure to the polybrominated diphenyl ether mixture DE-71 damages the nigrostriatal dopamine system: Role of dopamine handling in neurotoxicity. Exp Neurol 241:138-147.

Return to Table of Contents

Father's obesity could have epigenetic effects

A study partially supported by NIEHS found that newborns with obese fathers had significantly less DNA methylation of the insulin-like growth factor 2 (IGF2) gene. Since reduced DNA methylation of this gene is associated with a higher risk of developing certain cancers, the study findings suggest that a father's obesity could influence his child's future health.

The researchers looked for associations between preconceptional obesity and changes in IGF2 DNA methylation. They examined DNA from 79 newborns whose mothers participated in the Newborn Epigenetics Study during pregnancy and also gathered information about both parents using questionnaires and medical records.

Even after adjusting for several maternal and newborn characteristics, they observed a persistent inverse association between DNA methylation in the offspring and paternal obesity (beta-coefficient was -5.28, $P = 0.003$). The researchers say that the changes in DNA methylation could result from obesity-related factors, such as diet or having diabetes, that were not measured in the study.

Citation: Soubry A, Schildkraut JM, Murtha A, Wang F, Huang Z, Bernal A, Kurtzberg J, Jirtle RL, Murphy SK, Hoyo C. 2013. Paternal obesity is associated with IGF2 hypomethylation in newborns: results from a Newborn Epigenetics Study (NEST) cohort. BMC Med 11:29. [commentary].

Return to Table of Contents

SOD1 can repress respiration

An NIEHS-supported study reports that an enzyme important in protecting cells from free radicals also helps repress respiration in rapidly dividing cells. The results reveal how yeast and cancer cells may repress respiration in favor of aerobic glycolysis, or fermentation, to promote rapid growth.

The researchers studied Cu/Zn superoxide dismutase (SOD1), which is known to help protect cells against oxidative stress. Using the yeast *Saccharomyces cerevisiae*, they revealed a new function for SOD1 in repressing respiration. When glucose and reactive oxygen are present, the enzyme binds to the casein kinase 1-gamma homologs Yck1p and Yck2p, protecting them from degradation. Yck1p and Yck2p are essential for respiratory repression, as well as nutrient sensing. Together, oxygen, glucose, and reactive oxygen make up a single circuit that can repress respiration through SOD1/casein kinase signaling. These results suggest that SOD1 acts as a metabolic focal point for integrating oxygen, nutrients (glucose), and reactive oxygen to direct energy metabolism.

Citation: Reddi AR, Culotta VC. 2013. SOD1 integrates signals from oxygen and glucose to repress respiration. Cell 152(1-2):224-235.

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

Return to Table of Contents

Intramural papers of the month

By Aleksandra Adomas, Mallikarjuna Metukuri, Bailey Schug, and Ajeet Singh

- Structurally similar endocrine-disrupting chemicals use same mechanism to activate estrogen receptors
- Mac-1 is a novel surface receptor of inflammatory response
- Consequences of ribonucleotide removal by topoisomerase 1
- Early-life exposures linked to early menarche in Sister Study

Structurally similar endocrine-disrupting chemicals use same mechanism to activate estrogen receptors

In a recent study, NIEHS researchers demonstrated that endocrine-disrupting chemicals (EDCs) with similar structures tended to induce estrogen response element (ERE)-mediated activities using the same mechanism. These actions did not correlate with their known ligand binding affinities. Since EDCs interfere with the body's homeostatic control and alter normal development and reproduction, this finding helps scientists better understand how chemicals, such as bisphenol A, affect humans.

The authors used two estrogen receptor (ER) negative cell lines, HepG2 and HeLa, to analyze the effects of three groups of EDCs on the estrogenic ERE-mediated and AP1/Sp1-mediated responses of ERalpha and ERbeta. The EDCs were chosen based on the similarity of chemical structure and product class. Bisphenol compounds (Group 1) strongly activated the ERalpha ERE-mediated responses; Daidzein, Genistein, Kaempferol, and Coumestrol (Group 2) activated both the ERalpha and ERbeta ERE-mediated activities; and Endosulfan and Kepone (Group 3) weakly activated ERalpha. Using Ishikawa cells stably expressing ERalpha, the team determined that multiple EDCs can differentially induce endogenous ER target genes.

Apart from demonstrating the mechanistic importance of chemical structures, the data also raise the issue of whether multiple assays should be used to assess the potential activity of EDCs. **(MM)**

Citation: Li Y, Luh CJ, Burns KA, Arao Y, Jiang Z, Teng CT, Tice RR, Korach KS. 2013. Endocrine-disrupting chemicals (EDCs): in vitro mechanism of estrogenic activation and differential effects on ER target genes. Environ Health Perspect; doi:10.1289/ehp.1205951 [Online 5 February 2013].

Return to Table of Contents

Mac-1 is a novel surface receptor of inflammatory response

In a new study, NIEHS researchers, for the first time, identified the immune cell receptor Mac-1 as a novel receptor for viruses. This study will help researchers better understand the molecular mechanisms that regulate innate immune responses that occur during a viral infection. Prior to this report, the role of Mac-1 had only been established in bacterial infection and tissue damage.

A host's inflammatory response may be triggered by double-stranded RNA (dsRNA), a byproduct of viral infection. The authors showed that Mac-1, which appears on the surface of macrophages, binds to dsRNA.

The study also revealed two distinct signaling events following dsRNA recognition by Mac-1 in immune cells. Poly I:C, a synthetic dsRNA, activates inflammatory oxidative enzyme NOX2, a subunit of NADPH oxidase, to produce reactive oxygen species. Poly I:C additionally participates in the induction of proinflammatory cytokines in a Toll-like receptor 3-independent, but Mac-1-dependent, manner.

This research uncovers how macrophages recognize extracellular signals associated with virus infection and identify a potential therapeutic target for virus-related inflammatory diseases. It also offers a potential new direction in drug development. **(AS)**

Citation: Zhou H, Liao J, Aloor J, Nie H, Wilson BC, Fessler MB, Gao HM, Hong JS. 2013. CD11b/CD18 (Mac-1) is a novel surface receptor for extracellular double-stranded RNA to mediate cellular inflammatory responses. J Immunol 190(1):115-125.

Return to Table of Contents

Consequences of ribonucleotide removal by topoisomerase 1

NIEHS researchers, together with collaborators at Umea University in Sweden, have determined that topoisomerase 1 (Top1), an enzyme important for uncoiling DNA during replication and transcription, can also remove ribonucleotides incorporated into DNA during replication. Because it happens when normal ribonucleotide excision repair (RER) mediated by the RNase H2 is defective, the research has implications for understanding Aicardi-Goutieres syndrome, a rare autoinflammatory disorder caused by mutations in RNase H2.

Using yeast as a model system, the scientists studied strains that were genetically engineered to incorporate a large number of ribonucleotides into DNA, and were defective in RER, Top1, or both. In the absence of RER, Top1 incised the DNA backbone where ribonucleotides were present, thereby initiating the removal of about 5,000 ribonucleotides from the genome.

However, these Top1 incisions generate dirty DNA ends that must be processed further to complete DNA repair. This process creates the opportunity for adverse consequences, demonstrated by the authors to include mutagenesis, replication stress, and genome instability. Because the enzymes involved in processing ribonucleotides in DNA are conserved, the authors suggest that the genome instability resulting from Top1 cleavage at ribonucleotides in DNA may be relevant to Aicardi-Goutieres syndrome, and possibly to other autoinflammatory disorders. **(AA)**

Citation: Williams JS, Smith DJ, Marjavaara L, Lujan SA, Chabes A, Kunkel TA. 2013. Topoisomerase 1-mediated removal of ribonucleotides from nascent leading-strand DNA. Mol Cell 49(5):1010-1015.

Return to Table of Contents

Early-life exposures linked to early menarche in Sister Study

Sister Study researchers looked at factors associated with age at menarche, or first menstrual period, and found that several early-life exposures were associated with it starting at a younger age. This study provides additional evidence that early-life exposures may influence age at menarche and is the first to report an association with maternal pre-pregnancy diabetes.

The study included 33,501 women, aged 35-59 years when they enrolled in the Sister Study, a nationwide cohort of women with a family history of breast cancer. The research group estimated associations of self-reported exposures with menarche at age 10 or younger, 11, 14, and 15 or older, relative to menarche at 12-13 years. The group found that having low birth weight, having had a teenage mother, being firstborn, having ingested soy formula during infancy, and specific prenatal exposures — mother's smoking, diethylstilbestrol (DES), prepregnancy diabetes, or pregnancy-related hypertensive disorder — were associated with early menarche at 10-11 years. Soy formula was also associated with late menarche.

Animal studies have shown that early exposure to exogenous estrogens can alter pubertal timing, and this research corroborates those findings. The authors suggest that future studies should evaluate associations with other pubertal changes, as well as how these relationships contribute to observed associations between early menarche and disease, such as breast cancer later in life. **(BS)**

Citation: D'Aloisio AA, DeRoo LA, Baird DD, Weinberg CR, Sandler DP. 2013. Prenatal and infant exposures and age at menarche. Epidemiology 24(2):277-284.

(Aleksandra Adomas, Ph.D., is a research fellow in the NIEHS Laboratory of Molecular Carcinogenesis. Mallikarjuna Metukuri, Ph.D., is a research fellow in the NIEHS Laboratory of Signal Transduction. Bailey Schug studies health promotion and nutrition at Appalachian State University and is an intern in the NIEHS Office of Communications and Public Liaison. Ajeet Singh, Ph.D., is a visiting fellow in the NIEHS Laboratory of Molecular Carcinogenesis.)

Return to Table of Contents

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