



# Environmental Factor

Your Online Source for NIEHS News

June 2010

## NIEHS Spotlight



### [Birnbaum Unveils Strategic Vision for NIEHS](#)

On May 17, NIEHS/NTP Director Linda Birnbaum, Ph.D., provided employees and the public a vision for the Institute.



### [The Power of Partnerships](#)

NIEHS welcomed public health leaders from across the country to the inaugural Partnerships for Environmental Public Health meeting.



### [Council Looks Ahead During Spring Meeting](#)

The May 12–13 meeting of the National Advisory Environmental Health Sciences Council at NIEHS meant a busy day and a half for members.



### [Superfund Researcher Named Dartmouth Provost](#)

With her appointment as provost, NIEHS grantee and biologist Carol Folt, Ph.D., now holds the second highest position at Dartmouth College.



### [Birnbaum Addresses UT Houston Grads](#)

NIEHS/NTP Director Linda Birnbaum, Ph.D., addressed graduates of the University of Texas Health Center at Houston School of Public Health.

## Science Notebook



### [GEMS Meeting Highlights Tox21](#)

The Genetics and Environmental Mutagenesis Society spring meeting offered members an inside look at efforts to advance predictive toxicology.



### [P-glycoprotein — 800-lb Gorilla of the Blood-Brain Barrier](#)

Our attempts to treat diseases of the central nervous system are often complicated by inadequate transport of drugs and proteins.



### [Taking Air Pollution Studies to the Next Level](#)

Biostatistician Francesca Dominici, Ph.D., is developing novel models to better understand environmental exposures to complex mixtures.



### [RNA Translation and Motor Neuron Diseases](#)

In a May 10 talk at NIEHS, Paul Anderson, M.D., Ph.D., explored the delicate balance of protein translation, initiation, and repression.



### [New Insights into the Mysteries of Mitochondrial Disease](#)

Researchers in the NIEHS Mitochondrial DNA Replication Group report new findings on mitochondrial DNA (mtDNA) mutagenesis and depletion.

## NIEHS Spotlight



### [NIEHS Hosts Collins During NC Visit](#)

NIEHS staff extended a warm welcome to NIH Director Francis Collins, M.D., Ph.D., May 11–12 during his visit to North Carolina.



### [Collman Shines at UNC Award Talk](#)

Gwen Collman, Ph.D., delivered the keynote lecture after receiving the 2009 H.A. Tyroler Distinguished Alumni Award at her alma mater.



### [UC Davis Honors Superfund Researcher](#)

The University of California at Davis has awarded the Charles P. Nash Prize to Superfund researcher Ian Kennedy, Ph.D.



### [Senior Trainee Lands Independent Position at EPA](#)

Postdoctoral Fellow Brian Chorley, Ph.D., will leave NIEHS for an investigator position at the U.S. Environmental Protection Agency.



### [NIEHS and OSHA Lead Oil Spill Worker Safety Efforts](#) ▶ Video

NIEHS and OSHA are leading efforts to develop recommendations for the response to worker safety after the massive oil spill in the Gulf.



### [Balbus Spreads the NIEHS Message on Climate Change](#)

NIEHS Senior Advisor for Public Health John Balbus, M.D., engaged stakeholders during May on the topic of global climate change.

## Science Notebook



### [Fellows Host Wnt Signaling Expert](#)

Roel Nusse, Ph.D., a Stanford University professor and HHMI investigator, recently visited NIEHS as a guest of the LMC postdoctoral fellows.



### [Epigenetics, Early Development, and Adult Disease](#) ▶ Video

NIEHS Principal Investigator Trevor Archer, Ph.D., discussed epigenetics and its role in disease at an NIH forum April 29.



### [NIEHS Showcases Scientific Resources](#)

NIEHS scientists got a much needed opportunity to view a myriad of services available to them on Scientific Support Facilities Day April 28.



### [NTP Tackles Soy Infant Formula Safety](#)

The NTP Board of Scientific Counselors considered whether use of soy infant formula may cause adverse developmental effects in humans.



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

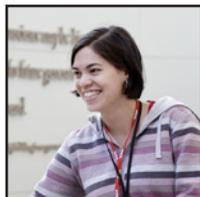
The news section of Environmental Health Perspectives looks at efforts to create standards to take green chemistry from principles into practice.

## NIEHS Spotlight



### [NIEHS Honored for Sustainability](#)

Representatives of the DHHS Green Champions Awards program offered NIEHS kudos for its accomplishments in sustainability.



### [Local Trainees Network at NIEHS Biomedical Career Fair](#)

The NIEHS Trainees Assembly kicked off the highly anticipated 13th Annual NIEHS Biomedical Career Fair April 30.



### [John Peters Remembered](#)

Friends and colleagues mourned the passing of John Peters, one of the legends of environmental and occupational health.

## Inside the Institute



### [Fun for All During Health and Fitness Week](#)

Many members of the NIEHS family turned out to exercise and have fun during Health and Fitness Week May 3-7.



### [Earth Sustainability Month at NIEHS](#)

Earth Sustainability Month activities during May gave NIEHS employees the opportunity to see sustainability in action at the Institute.

## Extramural Research

### [Extramural Papers of the Month](#)

- [New Concerns About Radiation and Breast Cancer](#)
- [Age Dependent Decrease in DNA Methylation Linked to Autoimmune and Heart Disease](#)
- [Prenatal Exposure to Phthalates Is Associated with Reduced Masculine Behavior in Boys](#)
- [Meta-Analysis Confirms Greater Asthma Risk from Asthmatic Mothers than Fathers](#)

## Intramural Research

### [Intramural Papers of the Month](#)

- [Gene Expression-Based Predictive Model for Hepatocarcinogenicity](#)
- [Periodontal Pathogen Infection Has a Potential Protective Effect in Asthma](#)
- [Oxidation State Alters Binding Affinity of Scaffolding Protein Involved in DNA Repair](#)
- [Novel Statistical Method for Testing Haplotype-Environment Interactions](#)

## Calendar of Upcoming Events

- **June 1** in the Executive Conference Room, 12:00–1:00 p.m. — Receptor Mechanisms Discussion Group with Julianne Hall, Ph.D., addressing “The Role of the Aryl-hydrocarbon Receptor in Mammary Differentiation and Disease”
- **June 2** in Rall F193, 10:00–11:00 a.m. — Laboratory of Neurobiology Seminar Series talk on “Synapses in Zebra Fish: A Model System of Nicotinic Transmission” by Fumihito Ono, M.D., Ph.D.
- **June 3** in Keystone 1003A/B, 10:00–11:00 a.m. — Keystone Lecture Series with John Rinn, Ph.D., speaking on “Large Intergenic Non-coding RNAs (lincRNAs): From Discovery to Mechanism”
- **June 3–4** in Keystone 2164/2166, Keystone 1003 AB, and Rodbell Auditorium, 8:00–5:00 p.m. — NTP High-Throughput Screening Workshop: Nuclear Receptor and Stress Response Pathway Screens
- **June 7** in Rodbell Auditorium, 10:30–12:00 p.m. — Michael Conn, Ph.D., speaking on “Healthy Environments: Natural and Scientific Ones”
- **June 7** in Rodbell Auditorium, 2:00–3:00 p.m. — Laboratory of Molecular Genetics Fellows Invited Lecture with Ivan Matic, Ph.D., speaking on “Modulation of Mutation Rates in Bacteria”
- **June 8** in Rodbell Auditorium, 10:30–12:00 p.m. — Seminar on “BRCA1 and Sirtuins in Genome Integrity, Cancer and Aging” by Chuxia Deng, Ph.D.
- **June 14–15** in Rodbell Auditorium, 8:30–5:00 p.m. — NTP Korean Symposium
- **June 17 (Offsite Event)** at the EPA, 8:30–5:00 p.m. — Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) Meeting
- **June 21–22** in Rodbell Auditorium, 8:30–5:00 p.m. — NTP Board of Scientific Counselors Meeting
- **June 30** in Rodbell Auditorium, 5:00–8:00 p.m. — Graduate Women in Science Rho Tau Chapter presentation by Susan Henning, Ph.D., on “Postnatal GI Development: The Journey from Steroids to Stem Cells”
- View More Events: [NIEHS Public Calendar](#)

## Birnbaum Unveils Strategic Vision for NIEHS

By Ed Kang

On May 17, NIEHS/NTP Director Linda Birnbaum, Ph.D., provided employees and the public a vision for the Institute. This roadmap for future research complements the priorities offered by NIH Director Francis Collins, M.D., Ph.D., just one week earlier during his visit to North Carolina ([see story](#)). Birnbaum's eight priorities focus on public health and prevention — themes with unique relevance for NIEHS (see text box).

Birnbaum emphasized the opportunities provided by the nature of NIEHS work compared to other NIH institutes. She noted that although NIEHS is a member of the NIH family and shares NIH's overall mission and priorities, “We focus on defining translation a little differently” than the other institutes and centers have in the past because of the emphasis by NIEHS on primary prevention.

As she explained, “Unlike the traditional focus of NIH on mechanism of diseases to find treatments and cures, our work is to find ways to prevent problems that affect public health.” She referenced the molecular, cell biology, and toxicology studies that provide the biological plausibility for understanding effects at the population level.

### A conceptual shift

“In the old days, we looked at high dose chemical toxicity — chemicals that overwhelm the body's defenses by brute force,” said Birnbaum, describing the shift within the scientific community in terms of understanding toxicity and exposure. However, she continued, “Chemicals can act like hormones and affect development at very low doses, and diseases can occur with very long latencies.”

The basis of these biological changes appears to be epigenetic. “Our genetics, epigenetics, and our environment all lead to our susceptibility to disease, toxicants, and drugs. The last decade was the decade of the genome, [but] we need to look at the next decade as the decade of the epigenome.”



*Birnbaum, shown at the podium in Rodbell Auditorium, was poised and optimistic as she outlined her vision for a new five-year strategic plan for NIEHS and NTP. (Photo courtesy of Steve McCaw)*

### The Eight Priorities of the NIEHS Strategy

- Understanding the effects of **low dose exposures**
- Determining how **windows of susceptibility** impact long-term health
- Developing **toxicology screening** methods like the Tox21 program that develops high throughput rapid screening approaches to multiple endpoints
- Examining how **mixtures of chemicals and multiple stressors** can alter our susceptibility and response
- Expanding the **clinical research** effort
- Characterizing the potential toxicity of **emerging hazards**, such as nano-engineered materials
- Exploring the **human health effects of climate change**
- Studying the impact of **green chemistry** on development of materials and processes

## From the first spark of an idea to a positive health outcome

The foundation for the director’s vision is the dynamic interrelationship among science, policy, and people, which Birnbaum described as the “science-to-policy continuum.” She said the best science builds on methods and data collection focused on diseases and issues, to inform policy related to prevention and public health. “We need to be involved in every step along this continuum — from the first spark of an idea to a positive health outcome,” urged Birnbaum.

Birnbaum completed her vision statement by outlining the status of new leadership hires, including the scientific director and director of the Division of Extramural Research and Training. She also outlined the NIEHS Strategic Plan for 2012 through 2016 and mentioned an opportunity for employees and the community to provide input as part of the planning process.

Finally, as a compelling appeal for conveying the relevance of the NIEHS vision, Birnbaum closed her remarks by challenging staff, in whatever role they have, “to understand how the environment can impact public health.”

(Ed Kang is a public affairs specialist in the Office of Communications and Public Liaison and a regular contributor to the Environmental Factor.)

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## The Power of Partnerships

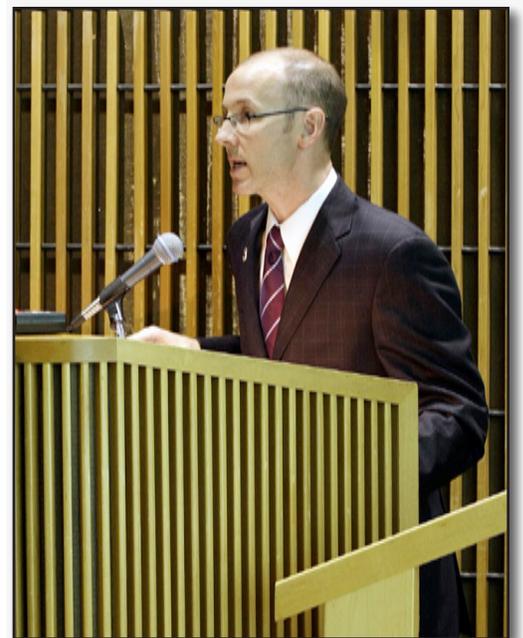
*By Thaddeus Schug*

Welcoming public health leaders from across the country to the inaugural [Partnerships for Environmental Public Health \(PEPH\)](#) meeting, NIEHS Director Linda Birnbaum, Ph.D., pledged her support for establishing and nurturing partnerships as part of achieving the NIEHS [mission](#).

The two-day event brought together more than 200 environmental health advocates, researchers, public health professionals, and community partners in a crowded Rodbell Auditorium at NIEHS April 26-27. Meeting planners organized the agenda into five main sessions that consisted of a mix of presentations, group discussions, workshops, and poster sessions.

Birnbaum told the participants, “I want you all to know how committed I am to this program, especially on issues of community engagement.”

Event host and NIEHS Division of Extramural Research and Training (DERT) Program Analyst Liam O’Fallon echoed Birnbaum’s vision for the PEPH program and said, “This is a new paradigm for the way NIEHS visualizes research. It is truly a program for the future.” He emphasized that PEPH demonstrates NIEHS commitment to supporting initiatives that bring communities and scientists together to work in partnership on environmental public health issues.



*O’Fallon, above, was well known to most of the attendees for his ongoing advocacy of environmental justice and community-based participatory research programs. He has led development of the new paradigm of PEPH over the past three years. (Photo courtesy of Steve McCaw)*

O’Fallon emphasized the significance of the meeting, “This event is the first time that so many grantees from different [DERT] programs have come together to share their individual and group accomplishments” ([see program list online](#)).

### **Engaging the community in environmental public health**

O’Fallon explained, “We developed PEPH to serve as an umbrella program for NIEHS activities in environmental public health. The aim is to build upon the strengths of past and current programs and to coordinate new and continuing activities in environmental public health with a focus on research, communication, capacity building, and evaluation.” Ultimately, the PEPH program will advance community engagement projects that will reduce adverse environmental exposures and prevent environmentally induced diseases and disability.

Meeting participants shared their personal perspectives on the importance of community engagement in environmental public health. Presenters highlighted the value of community participation, as well as the challenges that have to be overcome to achieve the desired project goals. Many participants noted the importance of fostering equitable partnerships and creating lines of effective communication between and among community residents and research organizations to meet environmental public health challenges.

### **Workshops offered a model in involvement**

The meeting’s five sessions and the Federal Coordination Panel embodied the theme of bi-directional engagement that Birnbaum and O’Fallon had mentioned in their introductions ([see text box](#)). Presenters gave informal talks that set the stage for a creative interchange of ideas, shared experiences, and suggestions from attendees. Moderated by PEPH working group members from DERT and some of the Institute’s grantees, the sessions helped give attendees a sense of group participation in an integrated, ambitious program to meet goals in their respective communities and programs.

At the meeting, the PEPH working group unveiled the PEPH Resource Center, a tool for grantees to share their educational outreach materials with one another and with NIEHS during a workshop on “Getting Acquainted with the PEPH Resource Center.”

Along with the information about programs and strategies, administrators were on hand to help grantees and potential [funding](#) applicants become better prepared to conduct successful, long-term programs in their communities.



*Birnbaum was met with rounds of applause during her talk, such as when she urged community engagement. “Not only do we need to do more research to inform, but we also have to empower our citizens so that they can work for changes in our environment that will lead to better health.” (Photo courtesy of Steve McCaw)*



*Hilton Kelley, representing the Community In-power and Development Association Inc., was one of several attendees who took advantage of an opportunity to thank Birnbaum for her support and to question her about the issues they face on the ground in their communities. (Photo courtesy of Steve McCaw)*



Steven Wing, Ph.D., a professor at the University of North Carolina at Chapel Hill, right, and Gary Grant, executive director of Concerned Citizens of Tillery, discussed disproportionate adverse impacts of industrial agriculture in Eastern North Carolina among people of color and lower economic status. (Photo courtesy of Steve McCaw)



Moderated by O'Fallon at the podium, the federal panel gave attendees an opportunity to learn what other funding mechanisms could be available to help support their programs. (Photo courtesy of Steve McCaw)



Collman, above, offered a summary and key messages at the end of the highly successful meeting. She said she looks forward to seeing the goals of PEPH furthered with the kind of supportive interaction that attendees enjoyed during the meeting. (Photo courtesy of Steve McCaw)

(Thaddeus Schug, Ph.D., is a postdoctoral research fellow in the NIEHS Laboratory of Signal Transduction.)

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## PEPH Workshop Sessions

- **Community Participation in Research: Insuring Research Leads to a Public Health Action**, followed by a poster session on CBPR, Building Capacity, and Novel Tools
- **Building the Capacity of All Research Partners**, sharing the strategies used by four programs to develop the capacity of key partners
- **PEPH Evaluation Metrics**, followed by a poster session on Community Outreach, Education, and Translation
- **Federal Coordination Panel**, which highlighted programs from NIH partner institutes and centers, the U.S. Environmental Protection Agency, the Centers for Disease Control and Prevention, and the National Institute for Occupational Safety and Health
- **Novel Methods, Models and Approaches Used to Detect Health Effects of Environmental Exposures**, presented by three leaders in the field
- **Risk Communication: Key Messages, Research, and Uncertainty**, a discussion by five communication experts

# Council Looks Ahead During Spring Meeting

By Eddy Ball

The May 12–13 meeting of the National Advisory Environmental Health Sciences Council (NAEHSC) at NIEHS meant a busy day and a half as members faced an agenda packed with new concept clearance proposals. Although they met their task with confidence and enthusiasm, the mood was tempered by concern over budget projections and the implications of the Gulf of Mexico oil spill. The meeting [presentations](#) showcased the accomplishments of the Institute’s extramural program staff, communications team, intramural research, and oil-spill response effort.

The meeting opened on an upbeat and positive note, as the group heard praise for the “remarkable scientists and leaders at NIEHS” and the Institute’s accomplishments from NIH Director Francis Collins, M.D., Ph.D., ([see story](#)). Midway through his talk, however, Collins described a looming budget shortfall in fiscal year 2011. Despite several promising developments at NIH, Collins cautioned the group, “Nothing changes the fact that we’ve got a cliff there,” as funding flattens or fails to keep pace with inflation and increased personnel [costs](#).

With a presentation at the end of their meeting on the NIEHS response in the Gulf, members were also reminded of potentially far-reaching effects on the environment and public health that are rapidly outstripping the meager resources available to responders.

Following Collins’ keynote address, NIEHS/NTP Director Linda Birnbaum, Ph.D., reported on the Institute’s recent accomplishments and progress toward realizing several important program objectives. Birnbaum’s discussion included her recent appearances before Congress, advances in the Institute’s climate change initiative, examples of outstanding NIEHS-funded research, the current report of the President’s Cancer Panel that for the first time focuses on environmental carcinogens, and the most recent addition to the NIEHS Bethesda office, Senior Medical Officer and Liaison to HHS Aubrey Miller, M.D.

Following the director’s report, members heard a presentation on the NIH [Basic Behavioral and Social Science Opportunity Network \(OppNet\)](#) by NIEHS Acting Susceptibility and Population Health Branch Chief and program liaison Claudia Thompson, Ph.D., and OppNet Coordinator William Elwood, Ph.D. According to the speakers, the program offers funding opportunities for researchers exploring the psychosocial aspects of the environment and the interaction of mechanisms of behavior, social functioning, biology, and environment that affect human health and wellbeing.



Collins gave members ample opportunity to ask questions about his hope that NIH can help transform “a sick-care system into a health-care system.” (Photo courtesy of Steve McCaw)



NIEHS Congressional Liaison Mary Gant queried Collins about his plans to ensure that environmental influences on microbiome-mediated health outcomes receive due consideration in research initiatives. (Photo courtesy of Steve McCaw)



Birnbaum had reason to be upbeat, as she reported on significant progress toward many of the objectives she outlined at Council meetings in 2009 in the months following her appointment as director. (Photo courtesy of Steve McCaw)

Most of the rest of the meeting was devoted to six concept clearance proposals by extramural program administrators that promise to build on existing grant programs in innovative and productive ways as well, as strengthen inter-agency and inter-division partnerships to maximize available resources. Council members remained engaged and supportive as extramural staff outlined their proposals, voting unanimously in favor of proceeding with each one of them:

- Human Health Impacts of Climate Change, by Caroline Dilworth, Ph.D.
- Dietary Influence on the Human Health Effects of Environmental Exposures, by Kim Gray, Ph.D.
- Small Business Innovation Research Contract Studies, by Daniel Shaughnessy, Ph.D.
- Consortium for NTP/FDA-Sponsored Toxicity Studies, by Jerry Heindel, Ph.D.
- Oceans and Human Health Funding Opportunity Announcements, by Fred Tyson, Ph.D.

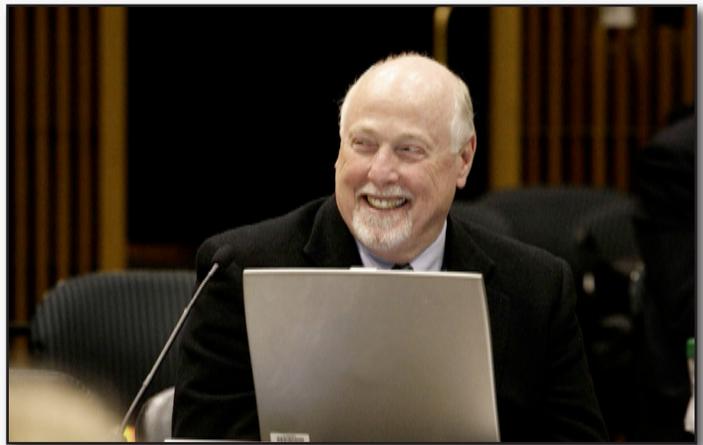
A science presentation by Laboratory of Pharmacology and Toxicology Chief David Miller, Ph.D., followed the extramural concept reports. Miller reported on the translation implications of his research into the blood-brain barrier on drug delivery, mitigating the effects of environmental exposures, and intervening in Alzheimer's disease ([see story](#)).

In a report that was as timely as the evening news, NIEHS Worker Education and Training Program Director Chip Hughes gave the final presentation of the meeting with a summary of his experiences as part of the "just-in-time" federal response effort to the massive oil spill in the Gulf. He conceded the effort may also be "just too late" to prevent long-term adverse effects on the health of residents and clean-up workers ([see story](#)).

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*Member Steven Lloyd, Ph.D., center, was so impressed by the Oceans and Human Health proposal that he suggested allocating even more funding to the program. Lloyd is a professor at Oregon Health and Science University. (Photo courtesy of Steve McCaw)*



*Member Hillary Carpenter, Ph.D., a toxicologist with the Minnesota Department of Health, said of the climate change concept, "This program could fill a real data need faced by state health departments." (Photo courtesy of Steve McCaw)*



*Responding to a request from the February meeting of Council, NIEHS Office of Communications and Public Liaison Director Christine Flowers described her team's accomplishments in raising the visibility of NIEHS and fine-tuning its communications strategies. (Photo courtesy of Steve McCaw)*

# Superfund Researcher Named Dartmouth Provost

By Eddy Ball

NIEHS grantee and biologist Carol Folt, Ph.D., now holds the second highest position at Dartmouth College, according to a May 5 press release issued by the college announcing her appointment as provost.

Among her many accomplishments, Folt served as the associate director of Dartmouth's interdisciplinary Superfund Research Program (SRP) from 1995 to 2010. She is a leading researcher in metal toxicity and the effects of dietary mercury and arsenic on human health, and she co-authored a significant number of the 133 publications associated with the college's NIEHS grant, "Toxic Metals in the Northeast: From Biological to Environmental Implications."

Earlier this year, Folt was elected as a fellow of the American Association for the Advancement of Sciences (AAAS) in recognition of her work in biology — the most recent in a long list of awards and honors. At Dartmouth, she also served as the dean of graduate studies, dean of the faculty of Arts and Sciences, and acting provost.

When he learned of his colleague's prestigious appointment, Bill Suk, Ph.D., director of the NIEHS SRP, described it as a great honor bestowed on a deserving individual. "Carol is an outstanding researcher and teacher, who received the Dartmouth Huntington Prize for excellence in teaching and research," he said. "She is also a good friend with a warm and engaging personality."

As provost, Folt will be directly responsible for overseeing the academic integrity of educational and research programs of the institution, including the three professional schools and School of Arts and Sciences, and for those operations that transcend the work of a single faculty, such as libraries, the museum, and the performing arts center.

In his announcement of Folt's appointment, Dartmouth College President Jim Yong Kim, M.D., Ph.D., said, "As Dartmouth's chief academic officer, Carol will play a crucial role in the institution-wide strategic planning process we are now launching. She brings an impressive record of academic leadership and vision and has the strong personal skills needed for this role."

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*Folt, above, has been a part of Dartmouth's SRP since it started in 1995. (Photo courtesy of Dartmouth College)*

# Birnbaum Addresses UT Houston Grads

*By Ed Kang*

To mark the 40th commencement of the [University of Texas Health Center at Houston](#) School of Public Health, NIEHS/NTP Director Linda Birnbaum, Ph.D., gave the keynote address May 8 before an audience of about 80 graduates and hundreds of family members, friends, and faculty gathered at the school's University Center.



THE UNIVERSITY of TEXAS  
HEALTH SCIENCE CENTER AT HOUSTON

She thanked the graduates for “embarking in this noble endeavor of seeking answers to some of humankind’s greatest health problems,” and went further to suggest, “You will be put to work on the biggest challenges the world has ever seen.”

## Challenges and the paradox of technology

On the one hand, she said, “The dark side of technology has been the impact of climate change on human suffering. [This] will be a primary influence on many of our public health concerns and will drive your work throughout your lifetimes.”

From her position as a career-long toxicologist, Birnbaum warned of another case of technology’s impact on our health — chemicals.

While acknowledging that “living without chemicals is just not possible,” she also pointed to ongoing biomonitoring studies by the Centers for Disease Control and Prevention that measure the presence of PBDE, bisphenol A, PFOA, acrylamide, perchlorate, phthalates, and nearly 200 other compounds found in people. “We are a walking cocktail of toxic or potentially toxic man-made chemicals,” she said.



*Birnbaum at the podium in Houston  
(Photo courtesy of UTH)*

## The promise of advanced laboratory analysis

“While the law of unintended consequences to our human activities is the law of the land, technology has the capacity to be a big part of the solution to characterize the public health issues, research the causes, develop solutions, and disseminate results,” she said, attributing the game-changing nature of supercomputers, the instant availability of huge quantities of data, and the analytical capability to bring meaning from that information.

Referring to the promise of advanced toxicological testing, Birnbaum told the graduates, “Today’s high-throughput assays do for wet chemistry what the semiconductor did for computing.”

## New demands on regulatory science

Continuing her theme of advancement, Birnbaum highlighted breakthroughs in the new science of epigenetics, the study of changes to the packaging of the DNA molecules that influence the expression of genes, and hence the risks of diseases and altered development. “This new understanding heightens the need to protect people at critical times in their development when they are most vulnerable — during ‘windows of susceptibility.’”

Birnbaum capped her address by offering a solution to bridge the divide between the damaging impacts of technological forces and the health benefits provided by certain cutting-edge advancements. “The current regulatory structure needs to be changed to embrace modern science and testing capabilities to better reduce risk,” she said, encouraging graduates to stay mindful of the continuum between science and policy. “Think broadly,” advocated Birnbaum. “Science isn’t done for the sake of science — your science should inform policy and regulations, and, likewise, good public policy should be based on strong and honest science.”

Bringing her remarks to a close, Birnbaum returned to the theme of environmental awareness, quoting Chief Seattle, leader of the Suquamish tribes in what is now Washington State. “You must teach your children that the ground beneath their feet is the ashes of your grandfathers. So that they will respect the land, tell your children that the earth is rich with the lives of our kin. Teach your children, what we have taught our children — that the earth is our mother. Whatever befalls the earth befalls the sons of the earth.”

(Ed Kang is a public affairs specialist in the Office of Communications and Public Liaison and a regular contributor to the Environmental Factor.)

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## NIEHS Hosts Collins During NC Visit

*By Eddy Ball*

NIEHS staff extended a warm welcome to NIH Director Francis Collins, M.D., Ph.D., May 11–12 during his visit to NIEHS and Clinical and Translational Science Awards (CTSA) programs at Duke University and the University of North Carolina at Chapel Hill, where Collins received his medical degree. Collins toured labs and the Clinical Research Unit at NIEHS and gave presentations to an all-hands meeting and to the National Advisory Environmental Health Sciences Council ([see story](#)).

After a morning spent meeting staff, talking with NIEHS principal investigators, and seeing examples of the research underway at the Institute, Collins addressed a standing-room only audience of employees gathered in Rodbell Auditorium.

### Birnbaum Honored by University of Rochester

Forty-three years after receiving her bachelor’s degree in biology from the University of Rochester, Linda Birnbaum returned to her alma mater to receive an honorary Doctor of Science degree. The presentation was held at the commencement ceremony for the School of Medicine and Dentistry May 14 in Kodak Hall’s Eastman Theatre on the campus. Distinguished physician [Benjamin S. Carson Sr., M.D.](#), director of the Division of Pediatric Neurosurgery at Johns Hopkins Medical Center, was also awarded an honorary degree.



*As the audience settled in for the town hall address, Collins, left, talked with Birnbaum. (Photo courtesy of Steve McCaw)*

NIEHS/NTP Director Linda Birnbaum, Ph.D., welcomed Collins back to North Carolina, as she joked about the high praise he's received in the press and television shows, such as the Colbert Report, for his ground-breaking research, his management of the massive human genome project, his success in communicating science to the general public, and his leadership of NIH.

For NIEHS employees, the visit was an opportunity to hear Collins speak about their Institute and its role in the larger NIH mission. For his part, Collins was clearly ready to establish rapport with his colleagues in North Carolina as members of the NIH family.

"You are a very important part of the National Institutes of Health," he said at the beginning of his talk, "and I hope you know just how much the work you do, the science you're invested in, is a central part of our vision.

"We're not going to change the genome any time soon," he continued. "The way we're going to help people is by modifying the environment." He added, "In fact, we can look at the NIH mission statement and [see that] it fits very nicely with what you're doing here."

Collins then launched a discussion of his five-part research agenda with its emphasis on bridging the gap between research and application. He introduced his first priority by observing that one of the exciting opportunities facing NIH is that "we are able to ask questions that have 'all' in them."

Collins discussed opportunities in genomics and other high-throughput technologies, translational research application, global health, enabling healthcare reform, and reviving and invigorating the biomedical research community. Near the end of his talk, Collins spoke of the impending funding cliff of post-stimulus flat budgets he anticipates for NIH institutes and centers in fiscal 2011, as funding increases will fail to keep up with costs in real dollars.



*Collins joined in the laughter as he sat in the audience during Birnbaum's introduction. He described some of the epithets people have used to describe him as "over the top," but he clearly enjoyed the good-natured humor. (Photo courtesy of Steve McCaw)*



*Prior to the town hall meeting, Collins, right, toured the NIEHS animal facility, talking and joking with NIEHS staff. Shown from left, are Biologist Greg Whitehead, Ph.D., Principal Investigator Don Cook, Ph.D., and Chief of Staff Paul Jung, M.D. (Photo courtesy of Steve McCaw)*



*Collins, right, toured several labs. He is shown, above, talking with NIEHS Macromolecular Structure Group Principal Investigator Traci Hall, Ph.D., center, and Postdoctoral Fellow Gang Lu, Ph.D.*



Collins, left, learned about work underway in the WormTox group headed by Principal Investigator Jonathan Freedman, Ph.D., right. The group conducts medium-throughput analysis of the effects of environmental stressors on nematodes. (Photo courtesy of Steve McCaw)



The final stop on the tour was the NIEHS Clinical Research Unit (CRU). Collins, right, discussed projects underway with NIEHS Acting Clinical Director Darryl Zeldin, Ph.D., and CRU Medical Director Stavros Garantziotis, M.D. (Photo courtesy of Steve McCaw)

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## Collman Shines at UNC Award Talk

By Robin Mackar

The passion that Gwen Collman, Ph.D., has for epidemiology shone as brightly as the sun in Chapel Hill April 28, as she delivered the keynote lecture after receiving the 2009 H.A. Tyroler Distinguished Alumni Award at her alma mater. The award is the highest alumni honor given by the University of North Carolina at Chapel Hill (UNC) Department of Epidemiology. Collman was honored for her work with the NIEHS Division of Extramural Research and Training, where she is currently acting director.

After a few brief introductory remarks by Aaron Fleischauer, Ph.D., UNC Epidemiology Alumni Association president, UNC Epidemiology Department Chair Andrew Olshan, Ph.D., reflected on his former colleague, Herman Alfred (Al) Tyroler, who made significant contributions to the field of epidemiology and is the namesake of the award.

Olshan commented that Tyroler had more than 40 years of service to the department, but it was his mentorship and enthusiasm for epidemiology that set him apart. From the excerpts of nomination letters Olshan read about Collman's commitment to fostering the careers of junior staff, it was easy to see why she was this year's recipient. "Gwen epitomizes what this award is all about, and we are extremely proud to have her as part of our extended UNC family,"



Collman shown at UNC with her 2009 H.A. Tyroler Distinguished Alumni Award (Photo courtesy of Amy Collman)

Olshan said, as he handed her the award and Collman took center stage in front of an audience filled with students, faculty, friends, colleagues, and family.

### **Grateful for mentors and early opportunities**

Before Collman began her formal lecture, she reminisced about coming to UNC in 1979, and how Tyroler and others in the Lipid Research Clinics program at UNC taught her about research from a variety of different perspectives. “I was just a kid, but they made me feel as important as any other investigator at the table,” said Collman. “I am grateful for the early experiences I had and the opportunities to learn about what it takes to pull together multi-site studies and publications. It helped set the stage for my later role with the extramural community.” She half-joked that her mentors were pretty clear on her career even before she was — she was going to get her Ph.D. What they didn’t realize was that her love for environmental epidemiology would win out over her initial interest in the cardiovascular field.

### **Community engagement in environmental epidemiology**

Collman’s formal presentation provided real life examples, data, and take-home messages about the commitment that she, the extramural staff at NIH, and NIEHS have about communities being an integral part of the research process. “Communities across the country have concerns about environmental hazards in their neighborhoods and how it affects their health and the health of their children and of future generations,” Collman said. This concern is the common theme that sets the stage for the field of environmental public health research, which NIEHS defines as the science of conducting and translating research into action.

## **NIEHS Community Engagement Initiatives**

Collman focused on three important NIEHS programs to illustrate the Institute’s commitment to channeling the power of community engagement into improving public health:

The [Breast Cancer and the Environmental Research Centers](#) are looking at the role of environmental exposures and genetics on pubertal development in young girls at three sites across the country. Collman noted there was a shift in literature indicating that girls were going through puberty earlier and that may be related to future breast cancer risk. She stressed the important role that breast cancer advocacy group members play in designing, implementing, and retaining participants in these studies, and mentioned that the advocates are especially helpful in working with the researchers to develop the key messages about the findings.

The [Environmental Justice Household Exposure Study](#) conducted by the Silent Spring Institute, the Communities for a Better Environment, and partners from Brown University is focused on knowing what communities are exposed to. Collman said she picked this example to show how the different groups work together with the community to report back findings. The study included going to 170 homes where air, dust and urine samples were collected. They looked at 150 compounds and developed some innovative user-friendly tools to communicate the findings to the individuals whose homes were included in the study.

The last example Collman gave her audience was the [CHARGE \(Childhood Autism Risks from Genetics and the Environment\) Study](#) at the University of California – Davis Center for Children’s Environmental Health. The uniqueness of this study is that a community advisory group was formed to engage the community in the study. The advisory group is comprised of parents of children with autism, adults who have autism, physicians who treat patients with autism, and scientists. Collman emphasized how the community wanted to first focus on looking at the controversial question about the link between mercury and the risk of autism. The data showed no link between the two. The advisory group was pleased that the investigators focused and published on this risk factor first, which helped set the stage for participation and acceptance of the study by the community.

“Some of the most interesting times during my career have been when community members have taken me in their cars or on walks to show me what their neighborhoods look like and what they are dealing with,” Collman said. She referred to these visits as “toxic tours,” which had a profound impact on her.

She discussed some of the many ways communities can be involved in research and then zeroed in on three specific examples of community engagement programs that highlight the NIEHS commitment to this area ([see text box](#)).

Collman closed with some lessons learned that indicate that partnerships between researcher and community members doesn’t involve compromising on the rigor of the work or the methods. Instead, she insisted, all of the parties at the table have something to learn and something to give to the research endeavor, and the joint experience adds to the richness of the work and to its translation.

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

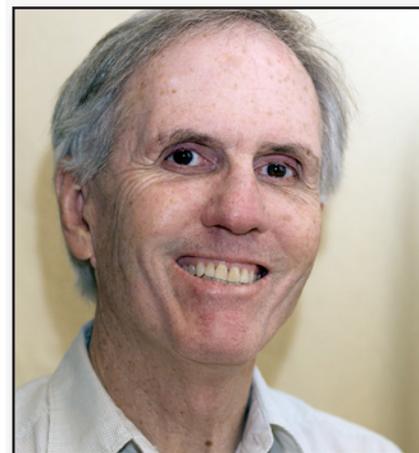
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## UC Davis Honors Superfund Researcher

*By Eddy Ball*

The University of California, Davis (UCD) announced April 26 that veteran NIEHS Superfund Research Program (SRP) researcher Ian Kennedy, Ph.D., has received the third annual Charles P. Nash Prize. The award committee honored Kennedy, a UCD professor of mechanical and aeronautical engineering for his “exceptional commitment to faculty advocacy and significant work in promoting faculty interests” as chair of the Davis Faculty Association.

Professor Bruce Hammock, Ph.D., director of the [NIEHS-funded Superfund Program at UCD](#) praised [Kennedy](#) for promoting interdepartmental collaborations. “For a quarter century Dr. Kennedy has worked to remove administrative barriers to interdisciplinary research,” Hammock said. “This is illustrated by his collaborative research evolving from combustion of toxic waste to one of the first federally funded programs in nanotechnology, to the use of nanotechnology in the design of biosensors for both environmental and medical technology.”



*Kennedy, above, was honored by his colleagues at UCD. (Photo courtesy of Bruce Hammock)*

One of Kennedy’s many collaborators, [NIEHS grantee](#) Isaac Pessah, Ph.D., a UCD veterinary molecular bioscience professor, stated, “Ian often has an innovative engineering solution for those of us trying to measure the unmeasurable.”

Kennedy has visited the NIEHS and U.S. Environmental Protection Agency Research Triangle Park campus several times to give seminars on his work. In 2008, he delivered a Superfund Research Program (SRP) Distinguished Lecture titled “Metal Oxides: Applications and Health” ([see story](#)). Last summer, Kennedy participated in the SRP-sponsored 11th International Congress on Combustion By-Products and Their Health Effects held at the U.S. Environmental Protection Agency, addressing “Engineered Ultrafine Particles for Health Effects Studies” ([see story](#)).

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# Senior Trainee Lands Independent Position at EPA

*By Sophie Bolick*

Postdoctoral Fellow Brian Chorley, Ph.D., will leave NIEHS for a coveted independent investigator position at the U.S. Environmental Protection Agency (EPA) this summer. As a recipient of an NIH Intramural Research Training Award (IRTA), Chorley spent the last five years with the Laboratory of Molecular Genetics (LMG) Environmental Genomics Group.

## Heading a research group at EPA

In his new position at the EPA, Chorley will head a research group functioning in a collaborative environment. He described the structure of the EPA as “more applied and team-oriented, with multiple principal investigators working on the same project.” Due to the nature of the specific problems EPA researchers work on, he said, “Negative data is just as important as positive data in determining whether a chemical is detrimental to human health.”

When asked about his short-term career goals, Chorley stated, “I would like to stay in this new position, grow as an investigator, and expand my program by eventually adding post-docs and biologists to the lab.” As his career evolves, he sees a possible transition from the bench to an administrative role. Because the EPA is an institution with a large regulatory component and an environment conducive to such career transitions, he has the opportunity to pursue basic science questions, answers to which can lay the groundwork for future policy and regulatory decisions.

## Building career development and networking skills

The combination of skills he developed while at NIEHS made Chorley a desirable candidate for the EPA position. He stressed that “fellows get experience which will help you if you want a specific job.” In addition to his research work ([see text box](#)), Chorley pursued interests in teaching, policy, and science communications by seeking out experiences that would give him familiarity with these fields. He was a regular contributor to the Environmental Factor for the past year and a half, developing a portfolio of nearly 20 feature stories. He also participated as a guest teacher during North Carolina DNA Day, and observed meetings of the Clean Air Scientific Advisory Committee.

As he balanced his research and career development activities, Chorley also recognized the importance of networking and getting involved. As a fellow, he interacted with some of the EPA scientists he will work with by attending local meetings of the Genetic and Environmental Mutagenesis Society (GEMS). Coordinating the LMG seminar series and organizing the annual retreat as a member of the LMG Trainee Action Committee provided valuable opportunities for interaction with internationally recognized scientists and scientific peers. Additionally, Chorley took advantage of opportunities to present his research findings at local and national meetings in the form of both invited talks and poster presentations.

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



*Along with developing his scientific career, Chorley, above, nurtured interpersonal and communications skills in the course of his training at NIEHS. (Photo courtesy of Steve McCaw)*

## At the Bench in NIEHS Labs

A native North Carolinian, Chorley received both his undergraduate and graduate degrees at North Carolina State University. His work on NRF2, a gene involved in oxidative stress, bridges work done in the LMG and Laboratory of Respiratory Biology (LRB). Chorley used a combination of bioinformatics and molecular biology approaches to identify putative functional Nrf2 binding sites in the human genome as he trained under the guidance of LMG Principal Investigator Douglas Bell, Ph.D. (LMG) and Steven Kleeberger, Ph.D., LRB principal investigator and acting deputy director of NIEHS.

Chorley advises fellows, “to learn front end skills yourself, because the EPA felt it important for me to communicate with the Bioinformatics Core in my new position.” Chorley’s findings on NRF2, an important player in cellular response to oxidative stress, have led to several exciting lines of research in the Environmental Genomics Group.

Chorley described Bell and Kleeberger as important influences on his training at NIEHS and supportive mentors. “Dr. Bell and Dr. Kleeberger always worked with me when I explored opportunities inside and outside the lab,” he said, “and I am grateful to them for the quality training I received here as well as their personal interest in my career plans.”

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## NIEHS and OSHA Lead Oil Spill Worker Safety Efforts

*By Eddy Ball*

As part of the federal government’s response to the massive [oil spill](#) April 20 in the Gulf of Mexico, [NIEHS](#) and the Occupational Safety and Health Administration (OSHA) are leading efforts to develop recommendations for worker safety during the clean up.

In a [presentation](#) to the National Advisory Environmental Health Sciences Council May 13, NIEHS Worker Education and Training Program (WETP) Director Chip Hughes reported on his team’s experiences on point along the Louisiana and Alabama coasts as part of the [Deepwater Horizon Unified Command](#).

Characterizing the response effort as “a finger in the dike,” Hughes outlined the ways his team and its federal partners have called upon the fruits of past training collaborations to provide emergency information on worker training and help mobilize experienced hazmat instructors from unions, universities, and community colleges across the Gulf Region and as far away as Massachusetts and Washington State.

Hughes said that responders are frustrated by a number of unknown factors, including the exact volume of oil involved, the composition



*According to Hughes, the British Petroleum Deepwater Horizon disaster is quickly outstripping available resources. (Photo courtesy of the Deepwater Horizon Unified Command)*

of weathered crude, the environmental and health effects of dispersants, air pollution impact, and how workers will be affected by pollutants through skin contact, inhalation, and ingestion.

As Hughes explained, the U.S. Department of Health and Human Services is participating in the U.S. National Response Team, providing consultation and support on public health surveillance strategies to federal and state partners, and developing informational resources through efforts by programs in the Centers for Disease Control and Prevention (CDC), NIEHS, U.S. Food and Drug Administration, Office of the Assistant Secretary for Health, Office of Public Health and Science, and Office of the Assistant Secretary for Preparedness and Response. They are supporting efforts by several other federal partners, including the U.S. Environmental Protection Agency, U.S. Department of Homeland Security, and U.S. Department of Labor.

In its initial response to the disaster, NIEHS posted its Gulf Coast Oil Spill Emergency Response and Cleanup Information on the WETP National Clearinghouse for Worker Safety and Health Training [Web site](#). In the following weeks, NIEHS WETP Director Chip Hughes worked with leaders of other agency programs to coordinate worker training and safety efforts on site.

WETP staff members Jim Remington and Ted Outwater deployed to command centers in Houma, La., and Mobile, Ala., in early May, where they joined colleagues from OSHA and British Petroleum coordinating field-training operations. At OSHA's request, the CDC's National Institute for Occupational Safety and Health (NIOSH) sent Captain Margaret Kitt, deputy director for program issues, to Louisiana to facilitate NIOSH technical assistance to OSHA and NIEHS.

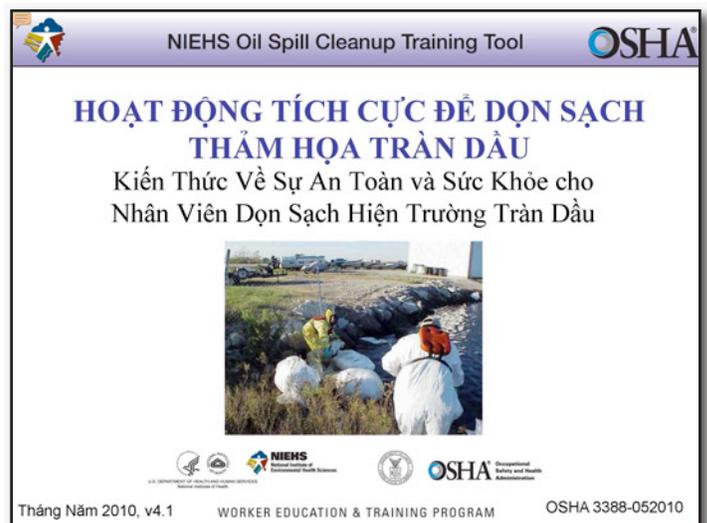
WETP staff and awardees quickly updated emergency support activation plans to be ready for deployment in the field. In Sarasota, Fla., NIEHS grantees at the Mote Marine Laboratory, funded through the Centers for Oceans and Human Health (COHH) program, added an oil-spill reporting tool to their existing [beach conditions report](#) that monitors conditions along the coast of Florida.



*Recalling the string of strategy meetings and the mood of participants, a somber Hughes showed the physical and emotional strain of the past weeks. (Photo courtesy of Steve McCaw)*



*Among the many sympathetic and concerned Council members was U.S. Navy Capt. Michael Macinski, who questioned pressure to waive health and safety standards during a disaster at a time when responders need them most. (Photo courtesy of Steve McCaw)*



*In addition to [safety booklets](#) in English and Spanish, Hughes and his team provided information in Vietnamese, above, to meet the needs of the population of Southeast Asians involved in fishing along the Gulf Coast. (Photo courtesy of WETP)*

Hughes closed his presentation with a statement about his hopes for the response effort that is unfolding on the Gulf Coast. “In remembrance of the eleven Deepwater Horizon drilling rig workers who died at MC252,” read his final slide, “may they not be forgotten.”

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## Balbus Spreads the NIEHS Message on Climate Change

*By Eddy Ball*

NIEHS Senior Advisor for Public Health John Balbus, M.D., engaged a diverse set of stakeholders during May on the topic of global climate change. Balbus made the important connection between global climate change and effects on human health for people who are just beginning to understand the importance of this aspect of global health, raising awareness of NIEHS and building a network of potential collaborators at home and abroad.

As part of the NIEHS global health team, Balbus spoke to pediatricians and public health academics in Canada and delivered the keynote address at the [Pediatric Academic Societies \(PAS\) Annual Meeting](#) on May 1. Later in the month, he served as the Department of Health and Human Services (HHS) representative on the U.S. delegation to the [United Nations Framework Convention on Climate Change \(UNFCCC\)](#) conference in Bonn, Germany, May 31–June 11.

In Vancouver, Balbus addressed hundreds of academic pediatricians in a talk titled “Putting a Human Face on Climate Change: A Public Health Perspective.” The following day he offered an update on children’s environmental health activities at NIEHS to attendees at the Environmental Special Interest Group meeting, where he had a chance to speak with Ruth Etzel, M.D., Ph.D., World Health Organization coordinator on children’s environmental health issues. Balbus also spoke to students and faculty at the schools of public health at The University of British Columbia and Simon Fraser University.

Back in the U.S., Balbus updated DHHS Assistant Secretary for Health Howard Koh, M.D., and others in the trans-DHHS climate change and human health workgroup in Washington, D.C. He also addressed the [CleanMed 2010](#) conference in Baltimore and a special workshop on climate change and respiratory health during the [American Thoracic Society International Conference](#) in New Orleans.

Looking ahead to Bonn, Balbus said, “I’m honored and excited to offer public health expertise to the U.S. delegation to the UNFCCC.” According to NIEHS/NTP Director Linda Birnbaum, Ph.D., this kind of higher visibility will help lay the framework for giving policymakers a fresh, human perspective on climate change, adding public health arguments for effective actions to limit climate change to the prevailing ecological, economic and diplomatic arguments.

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*Balbus, above, is an important part of the expanded NIEHS Bethesda-based liaison office. Birnbaum recently appointed Aubrey Miller, M.D., as NIEHS senior medical officer and liaison to HHS, and a search is underway for a liaison to the toxicological community. (Photo courtesy of Steve McCaw)*

# NIEHS Honored for Sustainability

*By Eddy Ball*

Representatives of the Department of Health and Human Services (HHS) Green Champions Awards program offered NIEHS kudos for its accomplishments in sustainability and awarded the Institute the 2009 Organization Green Champion Award. NIEHS Deputy Associate Director for Management Chris Long, NIEHS Sustainability Coordinator Trisha Castranio and NIEHS Environmental Awareness Advisory Committee (EAAC) co-chair Dick Sloane will receive the award at a ceremony June 10 at the Hubert H. Humphrey Building in Washington, D.C.

When she learned of the award, NIEHS/NTP Director Linda Birnbaum, Ph.D., said, “This is wonderful news, a credit to the leadership and dedication of the NIEHS Office of Management, and an honor for all the employees at NIEHS who are trying to make a difference in our sustainability efforts.” Appropriately, the announcement came just as NIEHS was celebrating Sustainability Month at its Research Triangle Park campus ([see related story](#)).

Each year, the HHS Green Champions Awards recognize and promote the excellence and creativity of HHS employees for their sustainability efforts in the areas of electronic stewardship, energy and water conservation, environmental management, green procurement, sustainable buildings, and transportation and fleet management.

The Organization Green Champion Award recognizes achievements of sustainability initiatives by efficient management practices and implementation of effective low-cost and no-cost programs. In addition to project successes, the award committee considers program and policy implementation that resulted in savings, financial or otherwise, expanded use of renewable energy, or better tracking of costs, investments, and savings.

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## Local Trainees Network at NIEHS Biomedical Career Fair

*By Erin D. Hopper*

The [NIEHS Trainees Assembly \(NTA\)](#) kicked off the highly anticipated 13th Annual NIEHS Biomedical Career Fair April 30. Designed to provide information about a wide range of professions for postdocs, the event included a combination of panel discussions, workshops, and networking opportunities.

As in previous years, the event took place in the Research Triangle Park U.S. Environmental Protection Agency (EPA) conference center. Throughout the day, the conference center was a flurry of activity as postdoctoral researchers and graduate students forged new relationships and gathered information about topics in career development.

Career Fair Committee co-chair Raj Gosavi, Ph.D., set the tone of the event with welcoming remarks before opening the floor to William Schrader, Ph.D., NIEHS deputy scientific director. Schrader emphasized the importance of networking and encouraged attendees



*Jensen stressed the importance of gathering information about what he calls OPE (Other People's Experiences). He emphasized that OPE is different from advice and pointed out that using OPE requires interpretation of the information learned and analysis of how it may be helpful to the individual in his or her own career development. (Photo courtesy of Steve McCaw)*

to meet as many people as possible throughout the day. Following Schrader's remarks, Julian Preston, Ph.D., associate director for health at the National Health and Environmental Effects Research Laboratory at the EPA, echoed Schrader's emphasis on networking, pointing out the challenges of competing with an increasing number of scientists for a limited number of open positions.

After an introduction by Gosavi, keynote speaker David Jensen shared his energy and excitement with the attendees during an engaging talk titled "Street Savvy Science: Aligning Your Career Goals with Job Market Realities." Jensen is the founder and managing director of CareerTrax, Inc., author and contributor to [AAAS Science Careers](#), and contributing editor and monthly columnist for [Contract Pharma](#) magazine.

Jensen began by describing the two worlds of academia and industry. He emphasized the differences in the application process for these two fields and noted that academia follows a very strict hiring process, while breaking the hiring rules often pays off in industry.

Above all, Jensen stressed the importance of networking and encouraged attendees to use the "peer+2" rule, in which a job seeker's networking efforts should be focused on individuals who are one to two years ahead of him or her in their own careers. Such individuals will have a better memory of their transitions out of graduate school or postdoctoral appointments and are more likely to be responsive due to stronger empathy for the job seeker's situation.

Following Jensen's talk, NIEHS Postdoctoral Fellow Heather King, Ph.D., noted, "This kind of practical, detailed information about the hiring process is exactly what we need to know but don't typically hear about." King also appreciated that Jensen's address taught attendees how networking "gets your resume out of the HR pile and onto the desk of a hiring manger."

The remainder of the event was designed to allow attendees to tailor the career fair experience to their individual interests. Participants could choose to attend various panel discussions, which were held during three separate sessions throughout the late morning and afternoon. Panel discussions covered topics ranging from traditional careers for postdocs, such as industry and academia, to non-bench careers, such as business/technology transfer, communication and outreach, regulatory affairs and policy, and clinical and translational research. A number of the panelists were past NIEHS trainees who were excited to share their own experiences with current trainees and students.



*Preston, right, listened intently as Jensen inspired career fair attendees to think outside of the box when searching for jobs. Career Fair Committee co-chairs Michelle Heacock, center, and Gosavi, left, sat in quiet observation as the culmination of their efforts began to unfold. (Photo courtesy of Steve McCaw)*



*A number of former NIEHS postdoctoral trainees returned to share advice with current trainees. Among them were former NIEHS postdocs Michelle Block, Ph.D., left, an assistant professor of anatomy and neurobiology at Virginia Commonwealth University and recipient of an NIEHS Outstanding New Environmental Scientist (ONES) grant, and Joel Meyer, Ph.D., an assistant professor of environmental toxicology at Duke University. (Photo courtesy of Steve McCaw)*

John Pritchard, Ph.D., NIEHS acting scientific director, concisely summarized the importance of the career fair in his letter to the attendees — “The NTA has provided each of you with a great opportunity to learn more about career options and to be much better informed than previous generations of scientists even a few years ago.” Pritchard concluded his letter by recognizing the hard work of the Career Fair Committee by saying, “The efforts that went into this Career Fair offer tangible evidence that our future is in good hands!”

## Career Fair Opportunities for Networking and Onsite Training

Throughout the day, career fair participants could choose to attend career development workshops on topics such as CV and resume preparation, interviewing skills, and professional certification programs. These workshops were expertly led by Lori Conlan, Ph.D., director of the Office of Postdoctoral Services at NIH, Diane Klotz, Ph.D., director of the NIEHS Office of Fellows’ Career Development, and Melanie Sinche, a career counselor and consultant at NIH.

One of the event highlights was the networking lunch, during which each attendee enjoyed dining with a chosen panelist in a small group setting. The lunch provided attendees with opportunities to learn more about a specific career trajectory and to make valuable contacts with like-minded peers. Various breaks throughout the day provided attendees with additional time to network with their peers and visit exhibitor booths to learn more about local organizations and companies.

This year also marked an expansion of last year’s efforts toward providing CV and resume review sessions for the attendees. A total of eight CV consultants from NIEHS, NIH, Duke University, and the University of North Carolina generously volunteered to spend the day meeting with attendees to give suggestions regarding the format and content of their CVs and resumes. In future years, the content of the career fair will continue to evolve to meet the ever-changing needs of developing scientists.



*The career fair offered ample opportunities for attendees to build relationships with fellow scientists. Between sessions, Kalina Rangelova, Ph.D., left, and Fiona Summers, Ph.D. of the Free Radical Metabolism Group at NIEHS share a laugh in the EPA rotunda. (Photo courtesy of Steve McCaw)*



*Bono Sen, Ph.D., science education and outreach program manager at **Environmental Health Perspectives**, provided advice to attendees regarding careers in science outreach. Sen, a former fellow at the EPA, learned a great deal from the NIEHS Biomedical Career Fair during her time as a fellow and was excited to return the favor as a panelist. (Photo courtesy of Steve McCaw)*

(Erin D. Hopper, Ph.D., is a postdoctoral fellow in the NIEHS Laboratory of Structural Biology Mass Spectrometry Group.)



*The Career Fair Committee, which was one of the largest in recent years, began organizing the event last September. Seated, left to right, are postdoctoral fellows Tracy Clement (NIEHS), Rebecca Heise (NIEHS), Ashley Godfrey (NIEHS), Erin Hopper (NIEHS), Melanie Fraites (EPA), Nisha Cavanaugh (NIEHS), and Lynea Murphy of EPA. Standing, left to right, are postdoctoral fellows Jorge Muñiz Ortiz (EPA), Jason Sampson (NIEHS), co-chair Gosavi (NIEHS), co-chair Heacock (NIEHS), Corinne Zeller-Knuth (NIEHS), Andres Larrea (NIEHS), David Draper (NIEHS), and Sophie Bolick (NIEHS). Not pictured are NIEHS postdoctoral fellows Sung-Yong Hwang and Jeffrey Sunman. (Photo courtesy of Steve McCaw)*

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## John Peters Remembered

*By Eddy Ball*

Friends and colleagues mourned the passing of one of the legends of environmental and occupational health after learning of the death May 6 of NIEHS grantee John Peters, M.D., D.Sc., whose research played a crucial role in demonstrating the short- and long-term effects of air pollutants on the health of children. Peters died at his home in San Marino, Calif., of pancreatic cancer at age 75.

Colleagues at the University of Southern California (USC) and nationwide expressed their deep sense of loss and extended their sympathy to Peters' widow, Ruanne, and family. Peters, the Hastings Professor and founding director of the USC Division of Environmental Health, was recognized as a leading authority in his field. Peters had been the principal investigator on a number of NIEHS grants and was the founding director in 1996 of its [the Southern California Environmental Health Sciences Center \(SCEHSC\)](#), directed by Frank Gilliland, M.D., Ph.D., since 2006.

USC posted an extended tribute on its [USCNews](#) Web site with comments by USC researchers Jonathan Samet, M.D., and Gilliland. The Los Angeles Times published a lengthy [obituary](#). The public health Web site [Pumphandle](#)

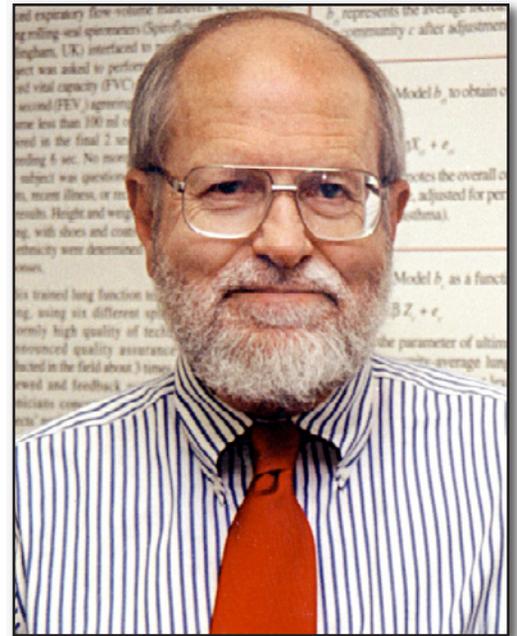
has posted a tribute that includes a heart-felt remembrance by Peters' longtime USC colleague and National Advisory Environmental Health Sciences Council member Andrea Hricko.

NIEHS/NTP Director Linda Birnbaum, Ph.D., described Peters' death as a great loss to the environmental health sciences community. In her response to the news, NIEHS Acting Director of Extramural Research and Training Gwen Collman, Ph.D., said of Peters, "He was a man of great vision and a delight to work with. He contributed to the field of respiratory epidemiology and air pollution in so many ways."

Peters founded the Children's Health Study in the early 1990s and mentored a team of investigators who continue to expand the scope of the original study. The study has shown that short-term exposure to pollutants increases asthma and absences from school, that children growing up and attending school near freeways suffer the worst effects from air pollution and that long-term exposure stunts the growth of the lungs.

During a productive 45-year career in the field of the environmental health sciences and public health, Peters published more than 150 research papers, reports and chapters on subjects including the health effects of air pollution, magnetic fields, asbestos, vinyl chloride and other chemicals in both the work and general environment. Last year, USC established the [John Peters Fund for Environmental Research and Education](#), which is accepting memorial contributions to sustain research and education in environmental health at USC.

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*Peters, above, was remembered by colleague and current SCEHSC director Frank Gilliland as "an example of scientific integrity [and] mentor for many of the current and future leaders in environmental health research." (Photo courtesy of USC)*

# Science Notebook

## GEMS Meeting Highlights Tox21

By Eddy Ball

During its spring meeting May 17 at the North Carolina Biotechnology Center, the [Genetics and Environmental Mutagenesis Society \(GEMS\)](#) offered members an inside look at ongoing efforts to advance predictive toxicology. The event featured a line up of speakers from NIEHS and NTP, NIH Chemical Genomics Center (NCGC), U.S. Environmental Protection Agency (EPA), and Hamner Institutes.

While the meeting looked forward to the new toxicology of the 21st century with the theme “High-Throughput Screening (HTS) for Chemical Genomics and Computational Toxicology,” members also had an opportunity to reflect on GEMS’ 27 years as a professional society. Midway through the meeting, attendees enjoyed an entertaining and inspiring talk by Larry Claxton, Ph.D., a retired EPA principal investigator, who was honored with a Lifetime Achievement Award for his contributions as a founding member and president of GEMS.

The meeting opened with welcome remarks from GEMS President and NIEHS toxicologist Jef French, Ph.D., and GEMS President-elect and EPA toxicologist Stephen Little, who organized and moderated the meeting. In his remarks, French said of the program, “I think it’s very timely.” He also noted, “The more things change, the more they remain the same,” as he referred to the recent report by the President’s Council on Cancer underscoring the need for continued research on environmental exposures and chemicals in the etiology and progression of cancer.

As presenters at the meeting observed, advanced screening methods using *in vitro* samples and *in vivo* alternative models, such as nematodes and zebrafish, in combination with state-of-the-art bioinformatics support, are helping researchers build massive, accessible libraries of data on compounds to support the goals of Tox21 — a consortium created by NCGC, NIEHS/NTP, and EPA in a 2008 memorandum of understanding. This new, trans-agency collaboration is anticipated to generate data more relevant to humans; expand the number of chemicals that are tested; and reduce the time, money, and number of animals involved in toxicity testing.



Speaker Windy Boyd, right, sat with NTP colleague Kristine Witt during Xia’s talk. Witt is part of the NTP High-Throughput Initiative and a longtime member and former officer of GEMS. (Photo courtesy of Steve McCaw)



Following the first round of speakers, Xia, center, spoke with Little, right, and retired NIEHS scientist Errol Zeiger, Ph.D., J.D., who is now a freelance science writer. (Photo courtesy of Steve McCaw)

The first speaker, [Menghang Xia, Ph.D.](#), group leader of Cellular Toxicity and Signaling at the NCGC, opened her talk on “Application of Quantitative High-Throughput Screening (qHTS) in Toxicological Studies at NCGC” with a review of developments that led up to the establishment of Tox21, especially the 2007 National Research Council report that called for a paradigm shift in toxicology testing. Xia described robot-assisted HTS using 1536-well plate format to screen as many as one million samples in seven days in the search for biochemical pathways *in vitro* that can predict adverse outcomes well in advance of traditional pathological endpoints.

The speakers who followed focused on components of the overall HTS and alternative method initiative and explained how their respective research agendas work in concert to promote the overall goals of Tox21 and the development of advanced predictive toxicology.

- NIEHS [WormTox Group](#) Senior Research Assistant Windy Boyd, Ph.D., who discussed the use of nematodes as a model organism in a talk titled “Caenorhabditis elegans in Medium-Throughput Toxicological Testing”
- EPA Toxicologist Steven Simmons, Ph.D., who explored efforts to use HTS to prioritize chemicals for more exhaustive testing based on activation of stress-response pathways in a talk on “Integrated Pathway Approach to High-Throughput Toxicant Identification and Characterization”
- Hamner Institutes toxicologist [Russell Thomas, Ph.D.](#), who described his experiments with alternative mouse models in a talk titled “Experimentally Defining Toxicity Pathways Using *In Vitro* High-Content Screening of Embryonic Fibroblasts from the Mouse Diversity Panel”
- EPA National Center for Computational Toxicology (NCCT) bioinformatician Richard Judson, Ph.D., who described advances in compiling two massive publicly available [databases](#) on compounds in a report on “ToxCast/ACTor HTS Informatics for Computational Toxicology Models”

As the meeting closed, attendees looked forward to another thought-provoking day-long meeting in the fall, which will also feature oral and poster presentations by students and trainees. GEMS fosters the training of the next generation of biomedical researchers through such professional development and travel awards to winners of the competition.



*French, left, said of the President’s Council on Cancer report, “Maybe there’ll be a renaissance,” as researchers use HTS to identify biological pathways related to development of cancer. During the morning break, he chatted with NTP toxicologist Raj Chhabra, Ph.D. (Photo courtesy of Steve McCaw)*



*As NTP Toxicologist Mike Cunningham, Ph.D., left, retired NTP scientist Barbara Shane, Ph.D., center, and Little showed, the breaks at GEMS meetings offer opportunities to discuss the talks, network, and set the stage for collaborations. (Photo courtesy of Steve McCaw)*



*As the final speaker of the day, Judson brought a sense of closure to proceedings as he described accessible databases that can be queried as scientists tackle the enormous backlog of untested chemicals by identifying early-stage biological perturbations linked to disease endpoints. (Photo courtesy of Steve McCaw)*

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*Little, right, posed with Claxton and his Lifetime Achievement Award. In his acceptance presentation, Claxton shared what he called “pearls of wisdom” from his career as a principal investigator. (Photo courtesy of Steve McCaw)*

## **P-glycoprotein – 800-lb Gorilla of the Blood-Brain Barrier**

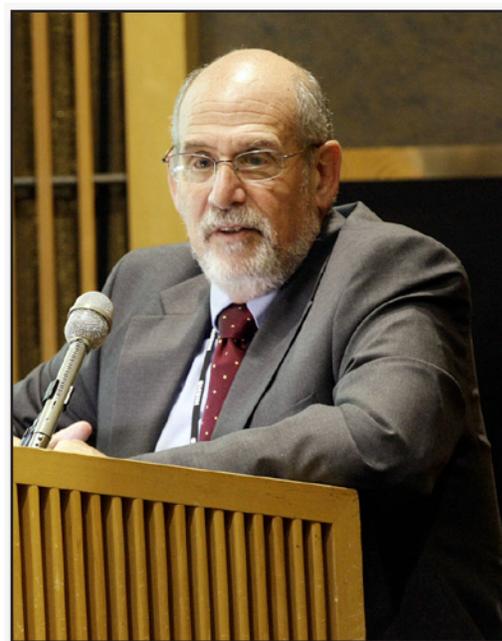
*By Thaddeus Schug*

Our attempts to treat diseases of the central nervous system are often complicated by inadequate transport of drugs and proteins to and from blood and neuronal tissue. That problem has inspired several recent investigations with potential translational impact from the lab of NIEHS Senior Investigator [David Miller, Ph.D.](#), who has explored the role of transport mechanisms in drug delivery efficacy, as well as the clearance of proteins implicated in Alzheimer’s disease.

Addressing the National Advisory Environmental Health Sciences Council (NAEHSC), and a crowded audience in Rodbell Auditorium May 13 as the meeting’s featured scientific lecturer, Miller explained, “Delivery of therapeutic drugs to the central nervous system is the major challenge of pharmacotherapy. This is due to the inability of many drugs to cross through a network of endothelium-lined capillaries that permeate the brain.”

In this context, Miller has focused on P-glycoprotein (P-gp), a protein responsible for limiting drug trafficking to the brain. Miller considers this transport protein the 800-lb gorilla of the blood-brain barrier (BBB).

Miller added that P-gp — an ATP-driven efflux pump — acts like a gatekeeper for the BBB by restricting numerous xenobiotics from



*Miller, who is chief of the Laboratory of Toxicology and Pharmacology, explains that understanding transporters of the BBB is essential to developing therapeutic strategies to treat diseases of the brain. (Photo courtesy of Steve McCaw)*

entering the brain. “The problem is the protein does not distinguish well between neurotoxicants and therapeutic drugs, so it is an obstacle to the treatment of a number of diseases, including brain cancer, epilepsy, and neuroAIDS,” Miller said.

### Xenobiotic exposures alter expression of transporters

Miller’s group has identified several ligand-activated intracellular receptors that increase expression of P-gp. “When activated, receptors such as the aryl hydrocarbon receptor (AhR), pregnane-X receptor (PXR), and constitutive androstane receptor (CAR), all of which are considered to be a major part of the first line of defense against toxicants, increase transport activity and protein expression for P-glycoprotein in brain capillaries.”

Miller used an *in vivo* brain-perfusion technique in rats to demonstrate that 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), which activates the AhR, increases expression of P-gp. TCDD-exposed rats became resistant to drug uptake in the brain due to the elevated transporter levels. “Exposure to toxins and xenobiotics tends to activate p-glycoprotein, making drug delivery to the brain even more problematic,” added Miller.

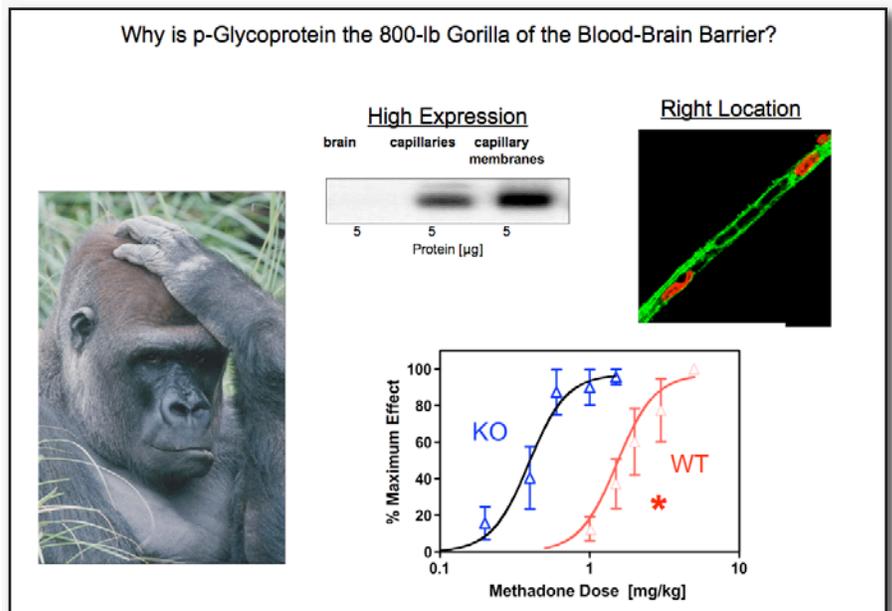


Acting Scientific Director John Pritchard, Ph.D., looks on as Miller informs the National Advisory Environmental Health Sciences Council about the progress of his research. (Photo courtesy of Steve McCaw)

### P-gp defective in Alzheimer’s disease

Miller then shifted gears to explain that P-gp also plays an important role in Alzheimer’s disease (AD). He hypothesized that buildup of the neurotoxic protein amyloid beta (A-beta) in AD patients may be due to defects in BBB transporter function. A-beta plaque formation is a contributing factor to the neural degeneration observed in AD patients. “In the normal situation, P-glycoprotein helps clear A-beta from the brain, so maintenance of transporter function is important,” added Miller.

Miller and colleagues found that BBB p-glycoprotein levels were reduced in an AD mouse model, the hAPP mouse. To determine whether they could rescue P-gp levels in these mice, they used PXR activation. Miller noted that treating the 12-week-old AD mice once a day for seven days with a PXR ligand restored P-gp levels in brain capillaries to those found in control mice. Importantly, brain A-beta accumulation in PXR-activated, hAPP mice was reduced by up to 60 percent.



Photos from his lab, clockwise from bottom left, illustrate why Miller considers P-gp the 800-lb gorilla of the BBB. According to western blot data, the protein is highly expressed in the critical location, as shown by fluorescent imaging of a capillary in the dense network surrounding the brain. P-gp expression affects the delivery of drugs, such as methadone, as shown in results of experiments with knock-out (KO) and wild-type (WT) animals, lower right. (Photos courtesy of David Miller)

Miller concluded that it is critical to determine whether long-term P-glycoprotein induction by oral dosing reduces brain A-beta levels, angiopathy, neurodegeneration, and cognitive impairment in the AD mice.

AD is the most common form of dementia in older people. It currently affects nearly 4.5 million people in the U.S. The risk of AD doubles for every five-year age interval beyond age 65, and as the U.S. population ages, a higher percentage of the population is likely to suffer from this debilitating disease. Miller's work could eventually provide a better understanding of the etiology of AD ([see related story](#)).

(Thaddeus Schug, Ph.D., is a postdoctoral research fellow in the NIEHS Laboratory of Signal Transduction.)

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## Taking Air Pollution Studies to the Next Level

*By Eddy Ball*

With a boost from [NIEHS support](#), Harvard University biostatistician Francesca Dominici, Ph.D., is laying the groundwork for developing novel models to help solve one of the persistent mysteries of public health — the effects of environmental exposures to complex mixtures.

Speaking to an at-capacity audience at NIEHS April 29, [Dominici](#) outlined the ways her work with two massive national databases covering 119 counties in the United States may help researchers pinpoint the health risks from the multiple individual components found in particulate air pollution mixtures. Dominici's talk, hosted by NIEHS Health Science Administrator Caroline Dilworth, Ph.D., drew epidemiologists, biostatisticians, and other scientists from NIEHS, as well as regulatory scientists from the neighboring U.S. Environmental Protection Agency (EPA), which also funds her research.



*During her introduction, Dilworth, shown at the podium, told visitors about the highly successful efforts of extramural administrators to showcase the talent of grantees through invited talks in the Keystone Lecture Series, which began in the fall of 2009. (Photo courtesy of Steve McCaw)*

A professor of biostatistics at Harvard School of Public Health, Dominici focuses on developing statistical methods for integrating and analyzing large heterogeneous datasets to estimate health risks and evaluate the health impacts of environmental regulations. She is an internationally recognized leader in statistical methodology and in the estimation of the health effects of air pollution, with several fruitful collaborations with NIEHS-funded scientists, including Outstanding New Environmental Scientist award winner Michelle Bell, Ph.D. ([see story](#)) Dominici was chosen to be the leading biostatistician in several Committees of the Institute of Medicine of the National Academies.

### **Air pollution poses complex health risks**

Dominici began her talk by reminding her audience, “We breathe a mixture.” Although researchers, especially regulatory scientists, have typically looked at single components in efforts to link a specific variable with a health effect, she said exposure is actually much more complex and involves multiple components with multiple

end points. In addition, within mixtures there may be additive, agonistic, and synergistic effects that could also influence how each component impacts health endpoints in different combinations.

By understanding multi-pollutant behavior more completely, Dominici explained, scientists can more effectively estimate risks, influence policies for controlling harmful air pollution, and design compliance strategies to reduce health effects of particulates. If she and her colleagues are successful, they may also help resolve some of the contradictory outcomes of earlier single-component research tied to single endpoints and better understand geographical differences in air pollution and health effects.

### Statistical size and power

Dominici will be working with two enormous data sets that she has used in [previous studies](#). One, the most recent version of the National Mortality, Morbidity, and Air Pollution Study (NMMAPS), contains daily mortality, air pollution, and weather data on conditions in 108 U.S. cities from 1987 through 2006. The other, the Medicare Cohort Air Pollution Study (MCAPS), contains information on billing claims for everyone over 65 in 204 U.S. counties from 1999 through 2008. According to Dominici, the data in the two studies amounts to several terabytes of information she can mine for association with the seven major components of the more than fifty chemicals that constitute fine particulate matter (PM<sub>2.5</sub>) by means of new hierarchical models, as well as novel methods to account for adjustment uncertainty in effect estimation and to check regression models for data in space and time.

As she neared the end of her presentation, Dominici acknowledged the challenges researchers face with this monumental task, such as uncertainty of selection cofounders and identification of sources for components of the mixtures. Still, she insisted, answering the question of how PM<sub>2.5</sub> components modify short- and long-term effects on mortality and morbidity is the key to translating 50 years of air pollution research into effective public health interventions.

“By identifying the toxicity of some specific agents in the mixture,” Dominici said, “we will guide the development of hypotheses on biological mechanisms of action that can be tested in experimental models, and we will better inform public policy.”

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*No stranger to the pitfalls of air pollution studies, Dominici said she hopes to better understand “how to properly average all of this information” about the effects of the different mixtures found in various parts of the U.S. (Photo courtesy of Steve McCaw)*



*Even front row seats were taken as scientists from the NIEHS and EPA campuses filled the room in the Keystone Building. (Photo courtesy of Steve McCaw)*

# RNA Translation and Motor Neuron Diseases

By Emily Zhou

In a May 10 talk at NIEHS, Paul Anderson, M.D., Ph.D., explored the delicate balance of protein translation, initiation, and repression. His seminar, titled “Polysomes, P-bodies and Stress Granules: Spatial Control of mRNA Translation/Decay,” described how protein translation repression is an important process that enables cells to modulate protein expression.

Anderson is the K. Frank Austen Professor at the Harvard Medical School and the associate chief of the Division of Rheumatology, Immunology, and Allergy at the Brigham and Women’s Hospital. He is recognized as an expert in post-transcriptional regulation of inflammatory cytokine production, translational initiation, and autoimmunity induced by environmental stressors. Both Anderson’s research and clinical work have advanced understanding of how RNA translation contributes to human disease pathologies. One of the exciting projects in his laboratory demonstrated the role of RNA translational repression in promoting motor neuron survival.



*“When eukaryotic cells are exposed to stress, one of the first things they do is to shut down general protein synthesis,” Anderson told his NIEHS audience. “This helps to conserve anabolic energy so cells can divert their energy to repair stress-induced damage.” (Photo courtesy of Paul Anderson and Harvard University)*

## Balance of translation initiation and repression

Anderson explained that protein translation in eukaryotic cells is delicately balanced by two opposing forces — translation initiation and translational silencing. Messenger RNA (mRNA) ready for protein synthesis is capped with 7 methyl guanine (7mG) at the 5’ end and occupied by a complex of initiation factors. This complex scans mRNA until it reaches the adenine-uridine-guanine (AUG) start codon, then releases initiation factors and binds ribosomes to allow protein translation. This process is balanced by translational silencing that involves a class of protein repressors to attenuate protein synthesis.

According to Anderson, translational silencing is constitutive in cells but can be aggravated under stress conditions, such as heat, oxidative stress, UV irradiation, and hypoxia. T-cell-restricted intracellular antigen-1 (TIA-1) protein, one of the translation repressors, assembles the untranslated RNA into stress granules (SGs), which consist of stalled translation complexes. Anderson has used immunofluorescent microscopy to demonstrate the formation of stress granules through arsenite insult in the cell cytoplasm.

## Complex composition of stress granules

Anderson argues that cells contain what he calls “mRNA triage” units that sort RNA between sites of translation initiation and sites of translation silencing. SGs determine RNA fate by selecting to degrade RNA, store RNA, or re-initiate translation.

SGs are composed of many different proteins that have functions in cell metabolism as well as cell survival. Anderson has identified genes required for the assembly of SGs using a genomic small interfering RNA

(siRNA) screen. He also discovered over 100 genes affected SG formation when knocked down, and most of these genes are involved in translation and protein signaling pathways. One such gene is RACK1. When expressed, *RACK1* is sequestered at SG where it inhibits stress-induced apoptosis.

### TiRNA, angiogenin, and motor neuron disease

Anderson's laboratory has recently discovered that a class of stress-induced small RNAs (tiRNA), natural products of cells, promotes translational repression. TiRNAs, which are 30 or 40 nucleotides in length, are formed through selective cleavage of transfer RNA (tRNA) by angiogenin — a 14 kilo Dalton (kDa) RNase that is secreted in response to hypoxia.

Angiogenin promotes motor neuron survival, and mutants of angiogenin are associated with the neural degenerative disease Amyotrophic Lateral Sclerosis (ALS). Anderson noted that a point mutation in the angiogenin gene reduces its ability to cleave tRNA and produce tiRNA. Both angiogenin and tiRNA are important in translation repression in cells exposed to environmental stresses. However, the mechanism by which tiRNAs inhibit protein synthesis is still under investigation.

Hosted by NIEHS Mammalian Aging Group Postdoctoral Fellow Thaddeus Schug, Ph.D., Anderson's seminar was the most recent talk in the NIEHS Laboratory of Signal Transduction Seminar Series.

(Yixing [Emily] Zhou, Ph.D., is a postdoctoral research fellow in the NIEHS Laboratory of Signal Transduction.)

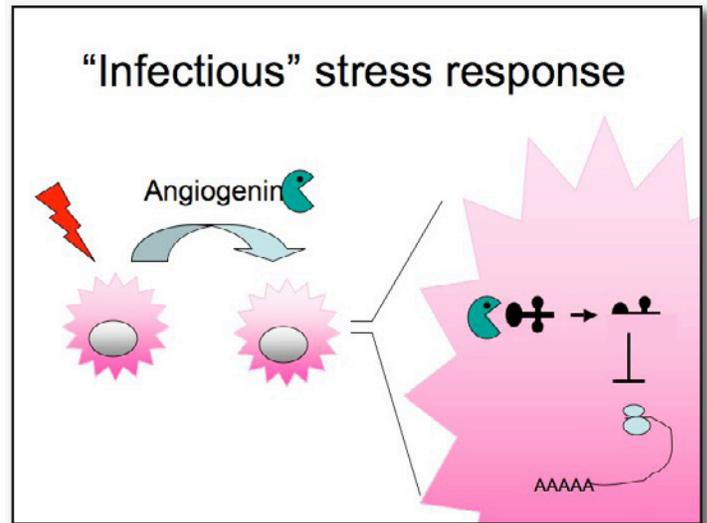
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## New Insights into the Mysteries of Mitochondrial Disease

*By Eddy Ball*

Researchers in the NIEHS [Mitochondrial DNA Replication Group](#) report new findings on mitochondrial DNA (mtDNA) mutagenesis and depletion in the journal *Human Molecular Genetics*. On the cover of its June 1 issue, the journal features a computer-generated crystal structure image used in the study.

The [study](#) advances understanding of mtDNA maintenance and points to potential strategies for predicting onset and intervening in the progression of the devastating diseases of the mitochondria.



*“Because stress-induced reprogramming of protein translation can help cells survive adverse environmental conditions, secreted angiogenin may activate an ‘infectious’ stress response program that allows stressed cells to warn their brethren of approaching noxious stimuli,” explained Anderson. “This may occur at the organismal level by secretion of angiogenin from the liver, or at the tissue level by secretion of angiogenin from stressed cells within peripheral tissues.” (Graphic courtesy of Paul Anderson)*



*First author Jeffrey Strumpf is a senior postdoctoral fellow in the Copeland lab. (Photo courtesy of Steve McCaw)*

According to the study's principal investigator, Bill Copeland, Ph.D., mitochondrial diseases remain one of the least understood and most intractable to treatment of all human disease.

Characterized by defects in energy production and related metabolic processes in the nervous system and organs of the body, "inherited mitochondrial diseases have a mortality rate roughly that of cancer, with very high rates of premature death," Copeland explained. Copeland is among several experts who speculate that inherited and induced mitochondrial defects may also contribute to the common diseases of aging, such as type 2 diabetes, Parkinson's disease, stroke, and Alzheimer's disease.

### Budding yeast offers clues to human mtDNA

Mip1, the mitochondrial DNA polymerase in the budding yeast *Saccharomyces cerevisiae*, is 43 percent identical to the human mitochondrial polymerase gamma, pol gamma. In their study, the researchers surveyed 31 mutations in *MIP1* that were identical to mutations found in mitochondrial disease patients and identified many with mtDNA defects *in vivo*. According to the researchers, of the 16 known human polymerases, only the *POLG*-encoded pol gamma is known to replicate DNA in the mitochondria.

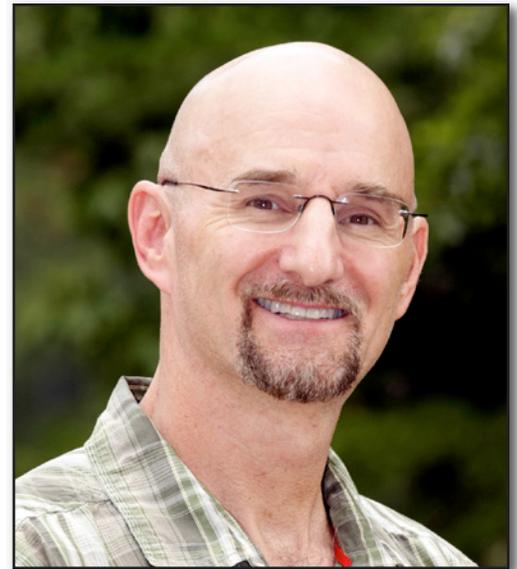
The research team characterized five sporadic mutations for the first time. Importantly, the scientists showed that increasing nucleotide pools by overexpressing ribonucleotide reductase (RNR1) suppressed mtDNA replication defects caused by several dominant mip1 mutations.

### Discovering potential interventions

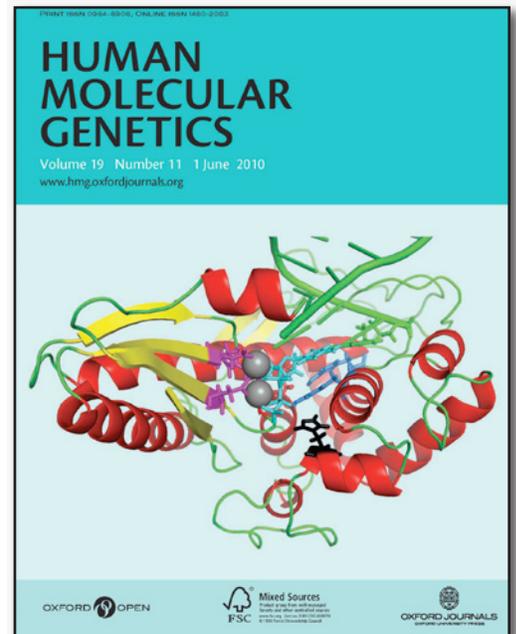
The team's experiments determined that the severity of reduced or depleted mip1 correlated with the age of onset of disease associated with defects in pol gamma, suggesting that targeted genetic testing might help clinicians in the future to identify disease in the early stages of development.

The researchers also speculated that overexpressing RNR1 increases mtDNA replication without triggering additional mutations. Thus, targeting RNR1 directly or indirectly could prove to be beneficial for patients by preventing onset or delaying progress of disease.

Copeland explains that by elucidating the mechanisms that promote mtDNA defects, researchers may ultimately discover clues to the role of environmental agents in causing genome instability *de novo* and among those individuals with genetic susceptibility, potentially informing primary prevention efforts to improve public health.



*Since joining Laboratory of Molecular Genetics in 1993, Copeland has tackled the mysteries of mitochondrial disease. His group's work on the replication fidelity of polymerase gamma established that spontaneous errors in this normally accurate polymerase cause 85 percent of mtDNA mutations. (Photo courtesy of Steve McCaw)*



*The cover image, above, shows the active site of the human DNA polymerase gamma highlighting the involvement of Histidine-932, in black, in deoxynucleotide triphosphate binding, shown in cyan. Substitution of tyrosine for histidine, due to a missense mutation that causes progressive external ophthalmoplegia and sensory ataxia mitochondrial diseases, disrupts deoxynucleotide triphosphate binding. (Photo and legend courtesy of Bill Copeland)*

## Support from NIH, NIEHS intramural program, and Summers of Discovery Program

Funding from the NIH, NIEHS intramural program, and NIEHS Summers of Discovery Program supported researchers in this latest study. In addition to Copeland, the team included the first author, NIEHS Postdoctoral Fellow Jeffrey Strumpf, Ph.D., of the Copeland lab, and Summers of Discovery students Diana Spell and Matthew Stillwagon. The NIEHS team collaborated with two investigators in the [Anderson Lab](#) at the Yale University School of Medicine — Principal Investigator Karen Anderson, Ph.D., and graduate student Christopher Bailey, who were supported by funding from NIH.

*Citation:* [Strumpf JD](#), [Bailey CM](#), [Spell D](#), [Stillwagon M](#), [Anderson KS](#), [Copeland WC](#). 2010. mip1 containing mutations associated with mitochondrial disease causes mutagenesis and depletion of mtDNA in *Saccharomyces cerevisiae*. *Hum Mol Genet*. 2010 Jun 1;19(11):2123-33. Epub 2010 Feb 25.

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## Fellows Host Wnt Signaling Expert

By *Sophie Bolick*

Roel Nusse, Ph.D., a Stanford University professor of Developmental Biology and Howard Hughes Medical Institute (HHMI) investigator, recently visited NIEHS as a guest of the Laboratory of Molecular Carcinogenesis (LMC) postdoctoral fellows. Speaking to a packed room on May 13, Nusse addressed “Wnt Signaling During Stem Cell Renewal and Tissue Repair,” focusing on several aspects of his extensive research on the protein’s influence on health and metabolism.

Hosted by Gilberto Dos Santos, a visiting fellow with the [Transcriptional Responses to the Environment Group](#), Nusse was the most recent distinguished scientist invited to NIEHS by the fellows, presenting his research as part of the LMC seminar series.



*Following his talk, Nusse, shown above, talked with postdoctoral fellows over lunch in the NIEHS Executive Conference Room. (Photo courtesy of Sophie Bolick)*

### Wnt signaling

Early in development, cells in a tissue respond to a given signal. As a tissue grows and becomes more complex, cells respond to the same signal in a different manner. Nusse likened this response to what is occurring with stem cells and explained, “Control over what stem cells are doing occurs locally. When you remove the niche, or signal, stem cells differentiate and lose their self-renewal state.”

Similar mechanisms are involved in tissue homeostasis following injury and adverse environmental exposure. Stem cells sense the loss of cells and become activated after damage, filling in the remaining tissue.

Nusse has spent many years studying the Wnt signaling pathway, which is involved in these processes. “When you follow Wnt signaling *in vivo*, there is a lot of fantastic stuff going on,” he said. Using a LacZ reporter mouse, he has studied active Wnt in stem cells in intestinal crypts, mammary glands, and lung, determining that stem cells *in vivo* are under control of Wnt signaling.

## Wnt sufficient for stem cell expansion in culture

Nusse said he wanted to answer an important question about stem cell expansion. “Now that we have purified Wnt protein, can we manipulate stem cells in culture using pure Wnt protein?” Addition of purified Wnt to embryonic stem (ES) cells in culture is sufficient for ES cell maintenance and expansion. Combining Wnt and the growth factor leukemia inhibitory factor (LIF) allows for several passages of the ES cells. When implanted in a mouse blastocyst, he explained, “The cultured ES cells are pluripotent and are able to repopulate the germ line of the mouse and generate whole animals.”

The mammary gland contains a population of self-renewing mammary stem cells (MSC), which can also be expanded in culture. In the presence of Wnt, there is a dramatic increase in the number of colonies that grow. Implantation of cultured MSCs in mice produces mammary glands capable of producing milk in lactating animals, Nusse said, “So these are bona fide stem cells.” The ability of single colonies to reconstitute into single organs is completely dependent on the Wnt program. “These studies may have value for organ regeneration,” Nusse explained.



Lecture host Gilberto Dos Santos (Photo courtesy of Steve McCaw)

## Wnt signaling is important in injury response

Nusse’s group also investigates the role of Wnt proteins in injury and repair of lung cells in mice. “The lung is a great tissue for studying injury and subsequent repair.” When mice are treated with naphthalene for 24 hours, Clara cells in the bronchioles are ablated. However, Clara cells regenerate and, seven days post injury, various Wnt family members are expressed. Normal ciliated cells adjacent to the ablated cells rapidly respond to the injury.

(Sophie Bolick, Ph.D., is a postdoctoral fellow with the Molecular and Genetic Epidemiology Group in the Laboratory of Molecular Carcinogenesis.)

## Active Wnt Proteins Are Modified by Lipids

Nusse has worked on Wnt biology since he discovered the *Wnt1* gene while working as a postdoctoral fellow in the lab of Harold Varmus, M.D., at the University of California, San Francisco. His career began in Amsterdam, the Netherlands, and has continued in both the United States and the Netherlands. Nusse is currently chair of the Department of Developmental Biology at Stanford University.

Nusse and his research group were the first to develop the first pure and active Wnt, Wnt3A. Purification of Wnts has led to the discovery that they are modified by the lipids palmitate and palmitoleate. Lipid modification makes Wnts hydrophobic and difficult to purify for functional studies. Since successfully establishing the purification protocol, Nusse’s lab has purified additional members of the Wnt protein family. With purified Wnt, functional studies could be done.

Lipid modification plays an important role in Wnt signaling. Using the fly as a model system, Nusse’s group has identified Secreted Wingless (Wg) Interacting Molecule (SWIM), which controls the effective range of Wnt signaling. Wg is the *Drosophila* homologue of Wnt, with both short- and long-range signaling functions. Mass spectrometry analysis demonstrates binding of SWIM to Wg by palmitate. Nusse points out “that the complex of SWIM and Wg is soluble in the absence of a detergent.” This finding, in combination with SWIM RNAi experiments showing that long-range target Distalles is perturbed, indicates long-range activity of Wg requires a soluble complex.

# Epigenetics, Early Development, and Adult Disease

By Laura Hall

April 29, NIEHS [Laboratory of Molecular Carcinogenesis](#) Chief [Trevor Archer, Ph.D.](#), presented an introductory talk April 29 to enlighten an audience of both scientists and non-scientists about epigenetics and its role in disease. The talk was part of a Staff Training in Extramural Program (STEP) event at the NIH campus in Bethesda, Md., titled “Blast from the Past! Early Influences on Long-Term Health.”

The forum focused on how epigenetic modification of gene expression, occurring during developmental periods in early life, can potentially affect long-term health and the issue of public health interventions.

As Archer explained, epigenetic changes in gene expression can be passed down through generations without changes in DNA sequence. The epigenetic change, which is often exposure induced, creates a phenotype or physical trait that does not follow the classical genetic inheritance rules of Mendel.

The epigenetic process can allow an induced change in gene expression that occurs in a grandmother to be inherited by her daughter or son as a fetus and influence the germ cells that will become her grandchildren.

Archer studies the structure and function of chromatin, which he defined as the combination of DNA and histone proteins that compacts and regulates the genetic material in each of our cells. “DNA can be made accessible for transcription, copying or repair by remodeling the compacted chromatin, altering the histone-DNA interactions within the chromatin subunits, called nucleosomes,” he explained. “However, it is the epigenetic marks that signal if gene activation or silencing will occur.”

The histone tails on chromatin can be modified by adding acetyl, methyl, or phosphate chemical groups. DNA can be modified by methyl groups. These modifications act like a code that gives stop and go signals for activating genes. Numerous enzymes and other proteins are involved. Archer categorized them as writers, readers, and erasers.

The writers modify histone by adding chemical groups, while readers are proteins with binding regions or motifs that recognize these modifications on DNA and histones. Erasers are enzymes that remove the modifications or marks, making these modifications reversible. This epigenetic code of marks on DNA and histone can promote or block gene transcription, thus affecting the proteins made as the downstream products of transcription.



*Changes in the epigenetic mark pattern can “change the transcriptional potential across the entire genome,” said Archer. (Photo courtesy of Steve McCaw)*



*NIEHS Chief Grants Management Officer Dorothy Duke is a member of the NIH STEP Forum Organizing Committee. She was one of the organizers of this event. (Photo courtesy of Dorothy Duke)*

Archer explained that the pattern of marks can be very complex, that multiple marks can occur with one nucleosome, and that there are multiple nucleosomes in each gene. These mark patterns change with development and cancer.

“Understanding how epigenetic information is deposited, maintained, and processed is key to understanding development and disease,” said Archer. The ability to reprogram cells by reversing or adding epigenetic modifications has “profound implications for therapeutics,” he added.

Archer’s talk introduced topics covered by the other speakers at the forum.

[Andrew Feinberg, M.D.](#), discussed how epigenetic control of tissue-specific developmental programming plays a role in common disease. Feinberg’s genome-wide DNA methylation studies show that colon cancer cells acquire a mixed pattern of methylation, combining features of normal colon and several other tissue types. Feinberg said, “This form of epigenetic confusion lies at the heart of cancer.” Key genes that regulate pattern formation and development had high levels of variability in their degree of DNA methylation, he explained, and that variability may explain disease.

[Kjersti Aagaard-Tillery, M.D., Ph.D.](#), studies fetal epigenetic changes that occur in the womb in response to maternal obesity and high-fat diet intake, maternal tobacco use, and environmental exposures. “Epigenetic alterations to the fetal genetic code reprogram expression of genes... [and] result in persistently altered risk of developing childhood and adult disease,” she said.

[Nancy Press, Ph.D.](#), an anthropologist, spoke about the ethical, legal, and social implication (ELSI) considerations in epigenetic research. There are unintended effects of scientific findings in terms of cultural perceptions and policy implications, according to Press. Epigenetic research studies will benefit from an awareness of, and practice in investigating, these effects.

(Laura Hall is a biologist in the NIEHS Laboratory of Toxicology and Pharmacology currently on detail as a writer for the Environmental Factor.)

## NIH STEP Forum on Epigenetics

All Department of Health and Human Services (HHS) employees were invited to the training forum, which was held at the Natcher Conference Center at the National Institutes of Health in Bethesda, Md. Many audience members participated through a live videocast, which was archived for DHHS employees at <http://videocast.nih.gov/Summary.asp?File=15877>.

### Speakers

#### **Trevor Archer, Ph.D.**

Chief, Laboratory of Molecular Carcinogenesis  
National Institute of  
Environmental Health Sciences  
“Introduction – Epigenetic Influences  
on Long-Term Health”

#### **Andrew P. Feinberg, M.D.**

Director, Center for Epigenetics  
Chief, Division of Molecular Medicine  
Johns Hopkins University School  
of Medicine, Baltimore, Md.  
“The Epigenetic Basis of  
Common Human Disease”

#### **Kjersti Aagaard-Tillery, M.D., Ph.D.**

Assistant Professor Obstetrics and Gynecology  
Baylor College of Medicine, Houston, Tx.  
“Developmental Origins of Adult Disease and  
Epigenetics: Programming the Fetal Epigenome”

#### **Nancy Press, Ph.D.**

Professor, School of Nursing and Department  
of Public Health, School of Medicine  
Oregon Health and Science University,  
Portland, Ore.  
“ELSI Perspectives on Epigenetics:  
A New Paradigm for Collaboration?”

# NIEHS Showcases Scientific Resources

*By Negin Martin*

NIEHS scientists got a much-needed opportunity to view a myriad of services available to them during the NIEHS Scientific Support Facilities Day April 28. The event highlighted services offered by the NIEHS Resource Centers and Core Laboratories ([see textbox](#)), whose missions are to provide support and training to the NIEHS community. The intramural investigators and their collaborators have the advantage of using these freely available resources to develop strategies and skills to thrive and to realize their goals.

Using different support facilities like pieces of a puzzle, an investigator can put together a comprehensive research approach rapidly and effectively. At each center, trained staff members are available to assist researchers with design and implementation of experiments. In addition to expert advice, investigators can take advantage of laboratory resources, supplies, reagents, and state-of-the art equipment available through core laboratories.

The idea for the Scientific Support Facilities Day was proposed by NIEHS scientists Robert Petrovich, Ph. D., and Jason Williams Ph. D. As the event organizer, Petrovich explained, “Many intramural investigators are not aware of the incredible resources available to them in the NIEHS Core facilities and centers. The event introduced many newly recruited researchers and trainees to the NIEHS support facilities and allowed them to interact with their expert staff.”

Petrovich took a creative approach to putting a face on NIEHS scientific resources. During the half-day event, a rolling slide presentation depicted each core’s mission, services and pictures of staff.

All scientific services have Web sites linked to the NIEHS Employee Web site.

(Negin Martin, Ph.D., is a biologist in the NIEHS Laboratory of Neurobiology Viral Vector Core Facility and a 2009 Science Communication Fellow with Environmental Health Sciences. She recently completed a postdoctoral fellowship with the NIEHS Membrane Signaling Group.)



*Petrovich, the event organizer, established the NIEHS Protein Expression Core in 2003 as part of the Laboratory of Structural Biology. Annually, the Protein Expression Core completes between 50 and 80 projects for NIEHS investigators. The latest addition to the technical services offered by the group is baculovirus-mediated transient transfection of mammalian cells. (Photo courtesy of Steve McCaw)*



*Williams, the head of the Protein Microcharacterization Core, provides the NIEHS community with the latest technology in mass spectrometry. (Photo courtesy of Steve McCaw)*

## Resource Centers

- **Biostatistics and Bioinformatics** – experimental design such as sample size, proper randomization and elimination of potential confounding factors; data analysis for gene expression, pathway analysis and molecular modeling
- **Computational Chemistry and Molecular Modeling** – protein structure/domain prediction; visualizing proteins, carbohydrates, RNA, DNA and lipid membrane
- **DNA Sequencing** – training in primer design, sequencing sample preparation and molecular techniques; sequence analysis
- **Flow Cytometry Center** – fluorescent-activated cell sorting and analysis
- **Fluorescence Microscopy and Imaging Center** – microscopy/imaging techniques; image analysis for co-localization, FRAP, FRET and TIRF
- **Microarray and Genome Informatics** – array-based data analysis, Next Gen Sequence data analysis, deletion mutant screening assay, transcription factor binding identification, data mining and computational data analysis
- **Next Gen Sequencing** – NIEHS Illumina sequencer at the NIH Intramural Sequencing Center facility at the National Human Genome Research Institute provides sequencing service

## Core Laboratories

- **Animal Resources**
  - **Quality Assurance Lab** – detection, isolation and elimination of pathogenic, microbial and chemical contaminants
  - **Veterinary Medicine** – training and assistance in rodent imaging, behavior phenotyping and surgery
- **Histology**
  - **Pathology** – histology, immunohistochemistry, electron microscopy, necropsy
  - **Special Techniques Lab** – mouse phenotyping, laser microdissection, digital image analysis graphics
  - **Clinical Pathology** – clinical chemistry, hematology
- **Knockout Mice** – generation of traditional and conditional knock outs and knock ins
- **Microarrays** – multiple microarray platforms; DNA methylation, chIP-chip analysis, array CGH, SNP arrays
- **Molecular Genetics** – resequencing, mouse tail genotyping and Illumina genotyping
- **Protein Expression** – optimizing protein expression using E.coli, baculovirus, or stable mammalian cell systems
- **Protein Microcharacterization** – mass spectrometry services including protein identification and post-translational modifications
- **Viral Vector** – design, production and validation of viral gene delivery using adenovirus, adeno-associated virus, lentivirus, retrovirus and sindbis virus

# NTP Tackles Soy Infant Formula Safety

By Mamta Behl

At its [May 10 meeting](#), the National Toxicology Program (NTP) [Board of Scientific Counselors \(BSC\)](#) took up the issue of whether use of soy infant formula (SIF) may cause adverse developmental effects in humans due to the presence of estrogenic isoflavones, also known as phytoestrogens. After nearly four hours of discussion, the BSC voted six to three to support the NTP Draft Brief on Soy Infant Formula conclusion of *minimal concern* for adverse effects on development in infants consuming SIF.

Kristina Thayer, Ph.D., acting director of the NTP [Center for the Evaluation of Risks to Human Reproduction \(CERHR\)](#), opened her presentation by describing the use of SIF. “Soy infant formula has been used for the past 60 years to replace or supplement use of breast milk or cow milk-based formula and now accounts for approximately 12% of U.S. infant formula sales,” explained Thayer. She further emphasized that infants fed SIF are exposed to significantly higher levels of genistein, the main phytoestrogen present in SIF, compared to those fed breast milk or cow-milk formula.

## Basis for NTP’s conclusion of *minimal concern* level of concern

The NTP assigned a level “2” to SIF on the five-level scale of concern used by the CERHR, with levels of concern ranging from “1” for negligible concern to “5” for serious concern. The basis for this conclusion stemmed from a combination of insufficient information from studies in humans to reach a conclusion on potential adversity, coupled with findings from laboratory studies demonstrating clear adverse effects on the female reproductive system in rodents exposed to genistein. Extrapolation of these results to human infants is complicated because the animals were treated with only one component of SIF.

“Although infants fed SIF can have total genistein blood levels exceeding those measured in neonatal or weanling rodents treated with genistein, the effects of genistein or its glucoside genistin may be very different when administered in SIF, which is a complex mixture of other isoflavones and non-isoflavone ingredients,” Thayer cautioned. Some of these mixture issues could be addressed through a series of animal studies being proposed by the NTP, presented to the BSC later in the day by Kembra Howdeshell, Ph.D., of CERHR.



*“The levels of concerns are determined on a case by case basis and integrate weight of evidence for developmental and reproductive effects in humans and laboratory animals with the extent of current human exposure levels as well as other factors that are often very specific to the chemical being evaluated,” explained Thayer, above, in response to members’ questions. (Photo courtesy of Steve McCaw)*



*Early in the discussion, Faustman, above, expressed her uneasiness about voting on acceptance of the report. “I would encourage the NTP to re-visit the guidelines for the definition of levels of concern.” (Photo courtesy of Steve McCaw)*

## Risk communication of the NTP Brief

One of the points of reservation expressed by members of the BSC and public spokespersons was the use of what some considered confusing language by the NTP. Some of the reviewers and public speakers, including Larry Williams, M.D., who represented the International Formula Council, pointed out that expressing “minimal concern” while also stating that SIF could “possibly affect human development” might create unnecessary anxiety for parents and confuse the general public. During the discussion, several members said that they felt the need for NTP to develop a more objective, precise, and consistent evaluation scale.

## Voting on the NTP Draft Brief on Soy Infant Formula

There was a lively discussion by the BSC on the extent to which the animal findings should be used to potentially raise concerns about the use of SIF, given its six decades of usage. Some panel members were reassured by the lack of reports of adverse effects in people who used soy formula during infancy. Others felt that the types of findings being observed in the animal studies had not been adequately assessed in humans.

The absence of reports of adverse effects does not necessarily mean they haven't or couldn't occur. Two prospective cohort studies of infants fed SIF are in early stages of development and will not generate results for several years — an NIEHS-funded Infant Feeding and Early Development Study (IFED) being conducted at the Children's Hospital of Philadelphia, and the USDA-funded Beginnings Study conducted by the Arkansas Children's Nutrition Center.

In the end, two-thirds of the members voted in favor of NTP classifying the risk level as minimal concern for adverse health effects from consumption of SIF by infants. Two members, Elaine Faustman, Ph.D., and Ruthann Rudel, said they felt the level of concern was too low, while the other opponent, James Sherley, M.D., Ph.D., said he considered the level of concern too high.

(Mamta Behl, Ph.D., is a research fellow in the NTP Toxicology Branch)

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## This Month in EHP

*By Eddy Ball*

The news section of the June issue of the NIEHS journal, [Environmental Health Perspectives \(EHP\)](#), examines issues surrounding what is known as greenwashing — advertising that promises more environmental benefit than a product delivers — as well as current efforts to create standards that could take green chemistry from principles into practice.



*Williams, who led off the public comment portion of the meeting, told the board, “SIF has been fed to more than 25 million human infants over the past 60 years with no known adverse effects.” (Photo courtesy of Steve McCaw)*



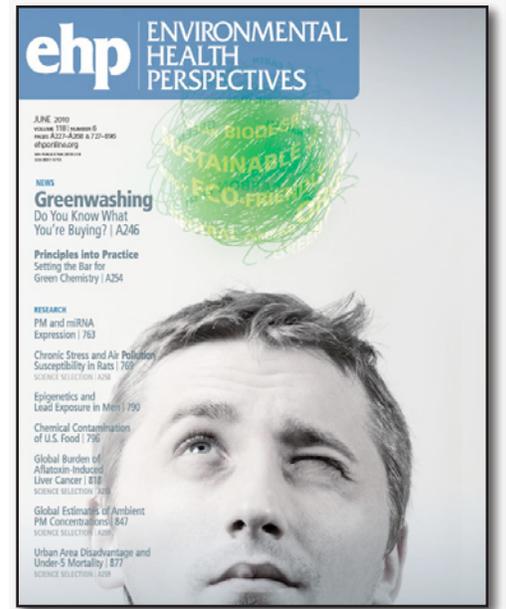
<http://twitter.com/ehponline>

The journal's [podcast](#) for June features an interview with NIEHS Epidemiology Branch Chief Dale Sandler, Ph.D., on what comes next for the groundbreaking Sister Study, now that recruitment of its cohort of 50,000 is complete.

Research highlights in the June issue include a review, Meta-Analyses and Neurotoxicants, and several new studies, including:

- Particulate Matter (PM) and miRNA Expression
- Chronic Stress and Air Pollution Susceptibility in Rats
- Epigenetics and Lead Exposure in Men
- Chemical Contamination of U.S. Food
- Global Burden of Aflatoxin-Induced Liver Cancer
- Global Estimates of Ambient PM Concentrations
- Urban Area Disadvantage and Under-5 Mortality

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## Extramural Papers of the Month

*By Jerry Phelps*

- [New Concerns About Radiation and Breast Cancer](#)
- [Age Dependent Decrease in DNA Methylation Linked to Autoimmune and Heart Disease](#)
- [Prenatal Exposure to Phthalates Is Associated with Reduced Masculine Behavior in Boys](#)
- [Meta-Analysis Confirms Greater Asthma Risk from Asthmatic Mothers than Fathers](#)



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

## New Concerns About Radiation and Breast Cancer

New research findings, funded in part by NIEHS, suggest that ionizing radiation exposure not only produces mutations that lead to cancer, but also changes the microenvironment of cells so that future cells are more likely to become cancerous.

Researchers used non-lethal but substantial doses of radiation much higher than what a woman would be exposed to during a mammogram, but approaching levels used in CT scans or radiotherapy.

Human mammary epithelial cells were used in the experiments. These cells line breast ducts where most breast tumors originate. They typically divide 5-20 times in culture. However, a variant phenotype of cells capable of dividing for many weeks spontaneously arises. Typically the variant phenotype lacks a tumor-suppressor protein called p16 and is much more susceptible to malignancy.

The experiments consisted of growing cell cultures from normal breast tissue for about one week. Then some of the cells were irradiated with a single low-to-moderate dose. Four to six weeks later, most of cells in both the irradiated and non-irradiated culture dishes had stopped dividing. However, the daughters of the irradiated cells formed larger and more numerous patches of cells with the variant phenotype.

The researchers conclude that the radiation exposure promoted the growth of pre-cancerous cells by making the environment that surrounds the cells more hospitable to their continued growth.

*Citation:* [Mukhopadhyay R, Costes SV, Bazarov AV, Hines WC, Barcellos-Hoff MH, Yaswen P. 2010. Promotion of variant human mammary epithelial cell outgrowth by ionizing radiation: an agent-based model supported by \*in vitro\* studies. Breast Cancer Res 12\(1\):R11.](#)

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## **Age Dependent Decrease in DNA Methylation Linked to Autoimmune and Heart Disease**

A research team at the University of Michigan Geriatrics Center reports that T cell methylation patterns are more sensitive to low folate and methionine nutritional levels in older as compared to younger individuals, causing aberrant gene expression related to autoimmunity and cardiovascular disease. These findings suggest that attention to proper nutrition, especially folate and methionine intake, may be particularly important in older people.

The laboratory that conducted this research studies the role that DNA methylation and chromatin structure play in regulating immune and cellular function, and how changes in chromatin structure contribute to problems characterizing autoimmune diseases and aging. T cell DNA methylation levels are known to decline with age. This leads to the activation of genes implicated in lupus-like autoimmunity and acute coronary syndromes. The cellular mechanisms responsible for the decrease in methylation are not known. However, maintenance of methylation is dependent on dietary micronutrients, including folate and methionine, and is also affected by homocysteine levels.

T lymphocytes from healthy individuals aged 22-81 cultured with low folate, low methionine, or high homocysteine showed demethylation and increased expression of two genes associated with autoimmunity and coronary disease. These changes were seen in the cultures from subjects beginning at age 50 and the effects increased with age.

*Citation:* [Li Y, Liu Y, Strickland FM, Richardson B. 2010. Age-dependent decreases in DNA methyltransferase levels and low transmethylation micronutrient levels synergize to promote overexpression of genes implicated in autoimmunity and acute coronary syndromes. Exp Gerontol 45\(4\):312-322.](#)

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# Prenatal Exposure to Phthalates Is Associated with Reduced Masculine Behavior in Boys

A team of investigators led by University of Rochester researcher Shanna Swan, Ph.D., reports for the first time that prenatal exposure to phthalates causes reduced masculine behavior in boys. This finding adds to the growing list of health effects associated with phthalates and other endocrine-disrupting compounds found in plastics.

Mothers whose urine had been analyzed for phthalates in mid-pregnancy completed a questionnaire that included the Pre-School Activities Inventory used to assess gender differences in play behavior. The results show that concentrations of dibutyl phthalate and diethylhexyl phthalate metabolites in the mothers' urine samples were statistically associated with decreased masculine play behavior in boys who were an average of 5 years old at the time of the assessment. There were no strong associations for any other phthalate metabolites, nor were there any associations with girls' play behavior.

These data suggest that *in utero* exposure to antiandrogenic phthalates may be associated with less masculine behavior in boys. Although based on a relatively small sample (N=74 boys), the overall findings exhibit concern that environmental chemicals have the potential to alter androgen-responsive neurologic development in humans.

*Citation:* Swan SH, Liu F, Hines M, Kruse RL, Wang C, Redmon JB, et al. 2010. Prenatal phthalate exposure and reduced masculine play in boys. *Int J Androl* 33(2):259-269.

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# Meta-Analysis Confirms Greater Asthma Risk from Asthmatic Mothers than Fathers

Results from a meta-analysis and systematic review of 33 studies published from 1966 to 2009 confirm that maternal asthma imparts a greater risk of offspring asthma than does paternal asthma. Many of the studies had reached this conclusion independently. However, there were some studies that reached the opposite conclusion. Given this disparity, the research team conducted the meta-analysis to determine the authenticity and size of the maternal effect.

These studies involved greater than 250,000 participants. The final conclusion is that children with asthmatic mothers were 3.04 times more likely to develop asthma than those with non-asthmatic mothers. Children with asthmatic fathers were 2.44 times more likely to develop the disease. The statistical significance of the trend disappeared with analysis of the studies in which asthma was diagnosed by a physician and when the children in the studies were 5 years or older. However, in all analyses, the trend that maternal asthma imparted a greater risk than paternal asthma remained the same.

The findings from this analysis are consistent with animal studies demonstrating that maternal exposures can induce asthma susceptibility in offspring, supporting the notion that additional research is necessary to elucidate the mechanism for this maternal effect.

*Citation:* Lim RH, Kobzik L, Dahl M. 2010. Risk for asthma in offspring of asthmatic mothers versus fathers: a meta-analysis. *PLoS One* 5(4):e10134.

(Jerry Phelps is a program analyst in the NIEHS Division of Extramural Research and Training.)

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# Intramural Papers of the Month

By *Laura Hall and Angelika Zaremba*

- [Gene Expression-Based Predictive Model for Hepatocarcinogenicity](#)
- [Periodontal Pathogen Infection Has a Potential Protective Effect in Asthma](#)
- [Oxidation State Alters Binding Affinity of Scaffolding Protein Involved in DNA Repair](#)
- [Novel Statistical Method for Testing Haplotype-Environment Interactions](#)

## Gene Expression-Based Predictive Model for Hepatocarcinogenicity

NIEHS scientists in the National Toxicology Program (NTP) have developed a gene expression-based predictive model to identify hepatocarcinogens.

The current high-sensitivity NTP protocol to test the toxicity and carcinogenicity of chemicals in two-year rodent bioassays is very expensive. Only a small fraction of the estimated 30,000 chemicals in widespread commercial use in the U.S. have been tested.

An accurate method that can screen chemicals to more rapidly identify potential human carcinogens is critically needed. To address this need, researchers with NTP developed pattern-recognition models based on rat liver gene expression changes induced by subchronic chemical exposure to differentiate hepatocarcinogens from non-hepatocarcinogens.

After training the models on gene expression elicited by a set of chemicals with known carcinogenic activity, the researchers were able to accurately predict the known hepatocarcinogenicity of an independent set of alkenylbenzene flavoring agents — even predicting that two alkenylbenzenes never tested for carcinogenicity would be weakly hepatocarcinogenic in rat at a certain dose level. The study also showed that exposure duration is a critical variable and that the 90-day exposure data gave more accurate predictions.

*Citation:* [Auerbach SS, Shah RR, Mav D, Smith CS, Walker NJ, Vallant MK, et al. 2010. Predicting the hepatocarcinogenic potential of alkenylbenzene flavoring agents using toxicogenomics and machine learning. Toxicol Appl Pharmacol 243\(3\):300-314.](#)

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## Periodontal Pathogen Infection Has a Potential Protective Effect in Asthma

NIEHS scientists demonstrated a connection between infection with the oral pathogen *Porphyromonas gingivalis* (*P. gingivalis*) and a decrease in the lung inflammatory response to inhaled allergen — a phenomenon that may be important in the pathogenesis of asthma.

The team of researchers infected mice with *P. gingivalis* using a surgically implanted chamber. The mice were sensitized with the allergen ovalbumin before or after establishment of infection to study the effects of the infection

on allergic airway inflammation and airway responsiveness, the two hallmarks of asthma. Oral pathogen infection prior to allergic sensitization led to decreased histological inflammation and reduced airway levels of the T-helper lymphocytes type 2 (Th2) cytokines interleukin-4, -5, -13, but had no effect on airway responsiveness.

In contrast, oral pathogen infection after allergic sensitization did not alter inflammatory endpoints, but led to reduced airway responsiveness. These data provide the first direct evidence of a regulatory effect of an oral pathogen on allergic airway inflammation and responsiveness.

A prior study by the research group demonstrated an inverse relationship between antibodies to two oral pathogens and asthma, wheeze, and hay fever in humans enrolled in the National Health and Nutrition Examination Survey (NHANES).

Together, these findings are consistent with the hygiene hypothesis which contends that fewer opportunities for infection have led to increases in asthma and other allergic diseases.

*Citation:* Card JW, Carey MA, Voltz JW, Bradbury JA, Ferguson CD, Cohen EA, et al. 2010. Modulation of allergic airway inflammation by the oral pathogen *Porphyromonas gingivalis*. *Infect Immun* 78(6):2488-2496.

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## Oxidation State Alters Binding Affinity of Scaffolding Protein Involved in DNA Repair

The repair of DNA lesions requires multiple enzymes whose activities are organized by scaffolding proteins. One such protein, X-ray repair cross complementing group 1 (XRCC1), plays important roles in both base excision repair (BER) and single strand break repair. NIEHS scientists have structurally characterized the molecular interface connecting the XRCC1 N-terminal domain (XRCC1-NTD) and the catalytic domain of a DNA polymerase, polymerase beta (Pol beta), that form part of the repair complex.

The scientists discovered that XRCC1 can exist in two different forms — a reduced structure observed previously, as well as an oxidized structure. The oxidized form has substantial changes in secondary structure, folding topology, and electrostatic surface associated with the formation of a disulfide bond.

The results showed that although most of the structural changes are not located on the Pol beta binding interface, the interaction was sufficiently altered so that the affinity of oxidized XRCC1 for Pol beta was increased by an order of magnitude.

The researchers note that oxidation-dependent affinity of XRCC1 for Pol beta is consistent with the response of BER to oxidative stress. They suggest that the redox state of scaffolding proteins plays an important role in DNA repair by causing changes in the structure of the repair complex.

*Citation:* Cuneo MJ, London RE. 2010. Oxidation state of the XRCC1 N-terminal domain regulates DNA polymerase beta binding affinity. *Proc Natl Acad Sci U S A* 107(15):6805-6810.

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# Novel Statistical Method for Testing Haplotype-Environment Interactions

NIEHS researchers developed a novel statistical method to study multiplicative interactions of many single nucleotide polymorphisms (SNPs) simultaneously in relation to an environmental exposure. In simulations, this new test respects the nominal Type 1 error rate, provides good power under a variety of scenarios, and appears resistant to exposure-related population stratification bias.

SNP variations of a gene's DNA sequence can cause functional differences in its protein product and may contribute to disease. A haplotype is a set of SNPs that are close together on the chromatid, making them likely to be inherited together and, thereby, statistically associated. The analysis of haplotype-exposure interactions is important for investigating the causes of common diseases.

The method uses families consisting of an affected offspring (either exposed or not) and two biological parents. Genetic variants that increase susceptibility will tend to have been transmitted too often to affected offspring. If the genetic variant and the exposure work synergistically to cause the disease, this tendency will be more pronounced among the exposed than the unexposed.

The new non-parametric statistical method is reasonably powerful, handles missing genotypes, retains validity under any genetic main effects, tolerates Hardy-Weinberg disequilibrium, and does not require the user to know or estimate candidate haplotypes.

*Citation:* [Shi M](#), [Umbach DM](#), [Weinberg CR](#). 2010. Testing haplotype-environment interactions using case-parent triads. *Hum Hered* 70(1):23-33.

(Laura Hall is a biologist in the NIEHS Laboratory of Toxicology and Pharmacology currently on detail as a writer for the Environmental Factor. Angelika Zaremba, Ph.D., is a visiting postdoctoral fellow in the NIEHS Laboratory of Signal Transduction Inositol Signaling Group.)

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# Inside the Institute

## Fun for All During Health and Fitness Week

By Laura Hall

Many members of the NIEHS family turned out to exercise and have fun during Health and Fitness Week May 3-7. NIEHS staff seeking exercise partners, serious competition, or just information on how to live a healthier lifestyle enjoyed activities they could smile about.

In addition to the competitions, there were seminars and classes, including the Bicycle Maintenance Clinic May 3 for those who bike to work or are interested in trying ([see related story](#)).

The competitions yielded impressive results. Congratulations to all the first place winners, those who placed, and those who joined in to compete.

(Laura Hall is a biologist in the NIEHS Laboratory of Toxicology and Pharmacology currently on detail as a writer for the Environmental Factor.)



Lars Pedersen came in first out of 39 runners in the “Rogathon” 5K Run. (Photo courtesy of Steve McCaw)

### First Place Winners

#### **Fitness 15,000 Program — “Taking Steps to Your Health”**

Out of 20 teams of three people, the Freedom Fries with 272,377 steps won first prize:

- Michelle Campbell
- Gary Pittman (most valuable player with 104,018 steps)
- Brian Chorley

*Individual with most steps overall*

VeeVee Shropshire with 126,909 steps

#### **“Rogathon” 5K Run — 39 runners**

*Overall Winner* — Lars Pedersen, 18:15

*First Place Female Runner* — Andrea Moon, 25:45

#### **Three-on-Three Basketball Tournament**

- Wes Brinson
- Sha-Mel Riggins
- Keith Holloway

#### **Basketball Shoot-Out**

Men’s Competition — Mark Rubino

Women’s Competition — Stephanie Bullock-Allen

#### **Football Throw Contest**

*Men’s Competition* — Derrick Vest, 70 points

*Women’s Competition* — Claudine Cates, 35 points

#### **“How Long Can You Hold Out”**

*Men’s Competition* — Lamar Shaw, 65 points

*Women’s Competition* — A’tondra Carree, 50 points

#### **Table Tennis Singles**

Jianjun Gao



*They're off! Participants began the 2 Mile Nature Walk. (Photo courtesy of Steve McCaw)*



*VeeVee Shropshire was on hand to make sure everyone started together and stayed safe during the 2 Mile Nature Walk and "Rogathon" 5K Run. Many volunteers helped with the activities. (Photo courtesy of Steve McCaw)*



*First Place Female Runner Andrea Moon (left) and Raj Gosavi (right) watched as NIEHS Associate Director of Management Marc Hollander awarded medals to the other winners. There were prizes for competitors in different age categories. (Photo courtesy of Steve McCaw)*



*The final battle was intense for a year's bragging rights as the Three-on-Three Basketball champions. (Photo courtesy of Steve McCaw)*



*The proud winners of the Three-on-Three Basketball contest — Keith Holloway (left), Sha-Mel Riggins (center), and Wes Brinson (right) with his son, Wes Brinson, Jr. — posed with their medals. "It was fun," said Holloway. "Hard, but fun." (Photo courtesy of Steve McCaw)*



*Dan Snyder (center) showed interested bike riders how to change a tire during the Bike Maintenance Clinic. (Photo courtesy of Laura Hall)*



*Two of the resident Canada geese families came to check out the action on race day. (Photo courtesy of Steve McCaw)*

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## Earth Sustainability Month at NIEHS

*By Laura Hall*

Earth Sustainability Month activities during the second and third week in May gave NIEHS employees the opportunity to go behind the scenes to see firsthand how energy and water are being conserved and waste is being handled at the Institute. NIEHS offered tours of the central utility plant, solar photovoltaic array, waste handling facility, and incinerator facility.

Most of the time, these conservation measures and most of the waste handling activities normally go unnoticed. However, in late May, facilities staff members were gratified to learn that NIEHS had won the 2009 Department of Health and Human Services Organization Green Champion Award for its comprehensive sustainability program ([see related story](#)).

During the central utility plant tour, NIEHS Operations and Security Branch Chief Mitch Williams told visitors about the ways NIEHS reduced its overall electricity usage by 10.3 percent and water usage by 25 percent through conservation measures during the first half of fiscal year (FY) 2010 relative to FY 2009.

The Institute retrofitted campus lighting with more efficient fixtures, installed a 34.5-kilowatt DC photovoltaic solar array on the B module roof of the main building, and made energy efficient adjustments of the temperature settings for the chilled water that cools campus buildings. Over the course of a year, the solar array alone has generated enough energy to power five homes for one year.



*Water is cooled as it falls down the cooling tower that serves as part of the chilled water system used to cool campus buildings. The off-site Keystone Building has its own heating and cooling systems. (Photo courtesy of Steve McCaw)*

NIEHS reduced water use through installation of low-flow toilet fixtures and waterless urinals and reduced demand for chilled water with lower temperature settings. In response to the severe drought of 2007, NIEHS installed faucet aerators, showerheads, and flush valves that reduced the water flow rates in the campus plumbing fixtures, cutting the total annual water use by approximately one-third.

In addition, a new reverse osmosis system for the central utility plant condenser water system is near completion. By filtering the water used in the NIEHS cooling system, the system reduces mineral deposits that cause scale buildup within the heat exchanger inside the plant chillers and make the equipment less efficient. Filtered water can circulate in the system for longer periods, reducing the need for 8.5 million gallons of city water and saving \$65,000 annually.

Also underway is a piping construction project that will allow the central utility plant to operate the chillers that cool the NIEHS and the neighboring Environmental Protection Agency (EPA) buildings more efficiently. Piping changes to the chilled water system allows for diverting water to different chillers, so they can operate closer to full load, where they are the most efficient.

NIEHS is currently investigating the possibility of using Durham County reclaimed or gray water in the condenser water system that is part of the campus cooling system, said Williams. If acceptable for the system, this gray water can replace the approximately 50 million gallons of potable city water used each year by the cooling towers serving the NIEHS and EPA campuses and save 40 percent of the current total NIEHS and EPA city water bill.

During the May 20 waste facility tour, Hazardous Waste Manager Paul Johnson explained how the waste management team safely handles, stores, and transports hazardous and non-hazardous waste at NIEHS. Johnson described the regulations and safety requirements that must be followed to ensure safe handling of the materials.

Environmental Compliance Officer Bill Steinmetz discussed how waste from NIEHS laboratories is incinerated and emissions are controlled using a wet scrubber. Biologist Cindy Innes, who went on both the waste facility and incinerator tours, said afterwards, “It was interesting to learn about how the operators work out the combination of different waste products, such as bedding and plastics, to keep the temperature of the incinerator in a precise range to maximize combustion efficiency and help control emissions.”

Many of the NIEHS efforts to promote sustainability are described in detail within the recently released NIEHS “[Sustainability Report](#)”.

(Laura Hall is a biologist in the NIEHS Laboratory of Toxicology and Pharmacology currently on detail as a writer for the Environmental Factor.)



*Cooling tower piping and valves transfer water into the cooling towers for chilling. The system uses water for heat transfer, like the refrigerant in a residential air conditioning unit. (Photo courtesy of Steve McCaw)*



*A variable speed drive, shown above, slows down water pump motor speeds to match the pumping needs thereby reducing electrical demand and power costs. (Photo courtesy of Steve McCaw)*



The anticipated completion and start-up time for the new reverse osmosis system, above, is July 2010. The white tubes hold the filtering media. (Photo courtesy of Steve McCaw)



Paul Johnson, right, told NIEHS staff on the waste handling facility tour about how waste is collected, evaluated, packaged, and then stored before disposal. The waste management team also collects some of the waste laboratory solvents and sends them to outside companies for use as fuel, he said. (Photo courtesy of Steve McCaw)



“There are a lot of intricacies about storing waste that we don’t think about from the lab, such as how they separate and store waste,” said Innes. NIEHS waste materials are stored in different areas of the waste handling facility depending on their hazard characteristics. The door, above, leads to one such area. (Photo courtesy of Steve McCaw)



**NIEHS**  
National Institute of  
Environmental Health Sciences

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES  
National Institutes of Health

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