



NIEHS Spotlight



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Superfund and EPA Host Combustion By-Products Congress

A cross disciplinary group of scientists gathered June 1–3 at the U.S. Environmental Protection Agency (EPA) in Research Triangle Park, N.C. for the 11th International Congress on Combustion By-Products and Their Health Effects. [...read more](#)



Hrynkow Honored for Mentoring

NIEHS Associate Director Sharon Hrynkow was one of two NIH women scientists honored by the Bethesda chapter of the Association for Women in Science (AWIS) with the organization's annual Award for Excellence in Mentoring. [....read more](#)



NIEHS at Endocrine Society Meeting

NIEHS continues its tradition of having an impressive presence at the Endocrine Society's Annual Meeting. [....read more](#)

Science Notebook



Nuclear Compartmentalization Affects Gene Activity

According to Harinder Singh, Ph.D., the NIEHS Distinguished Lecturer for June, the mammalian immune system protects the body from a plethora of microscopic invaders, and is also an excellent model for examining fundamental questions in molecular, cell and developmental biology. [...read more](#)



Jordt Extends ONES Research on TRPA1 in Study on Asthma

Leading a 15-person team of researchers, NIEHS Outstanding New Environmental Scientist (ONES) awardee Sven-Eric Jordt, Ph.D., reported new findings on the role of sensory neuronal ion channel activation in producing airway inflammation and hyperactivity in asthma. [...read more](#)



New Study Links Intestinal Inflammation to Systemic Genotoxicity

Researchers at the University of California, Los Angeles (UCLA) have shown for the first time that intestinal inflammation is linked to systemic DNA damage in mice... [....read more](#)



LSU ONES Awardee Links Protein Misfolding to Ultrafine PM

On June 2, NIEHS grantee Stephania Cormier, Ph.D., spoke as part of the Organics and Free Radicals Session of the 11th International Congress on Combustion By-Products and Their Health Effects at the Environmental Protection Agency conference center in Research Triangle Park, N.C. [....read more](#)

NIEHS Spotlight



Birnbaum Speaks at Green Chemistry and Engineering Conference

NIEHS and National Toxicology Program (NTP) Director Linda Birnbaum, Ph.D., was one of four

distinguished participants in a panel discussion, “Design Signals from Environmental Health Sciences: What Every Chemist Should Know,” June 24 in College Park, Md. ...[read more](#)



NIEHS at WHO Conference on Children’s Health

NIEHS Superfund Research Program (SRP) Director William Suk, Ph.D., and SRP Program Administrator Claudia Thompson, Ph.D., were among 450

attendees including researchers, non-governmental organization (NGO) representatives and health ministers at the the third World Health Organization (WHO) International Conference on Children’s Health and the Environment, held in Busan, Republic of Korea June 7–10. ...[read more](#)



Autism Research Network Launches Major New Study

With financial support from NIEHS, three other NIH institutes and the private non-profit Autism Speaks, on June 9 a network of leading autism

researchers from three regions across the country launched one of the largest research studies of its kind to investigate early risk factors for Autism Spectrum Disorders (ASD) during a phone-in press briefing. [read more](#)



Institute Staff Supports Intramural Colleagues at Board Review

Staff from throughout the Institute showed up to support their intramural colleagues June 15–16, as the NIEHS Epidemiology

Branch and Fred Miller, M.D., Ph.D., presented their scientific findings and future plans during the Division of Intramural Research Board of Scientific Counselors (BSC) Review of the two programs. ...[read more](#)

Science Notebook



Findings Show Protection Against Oxidative Stress

High levels of reactive oxygen species (ROS) are implicated in cardiovascular and neurodegenerative disease and are proposed to accelerate aging

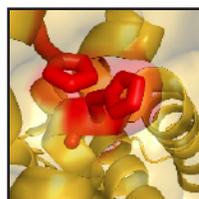
and promote cancer, according to new NIEHS-funded research published in *PLoS Genetics*. ...[read more](#)



Expert Panel Reviews Glass Wool Fibers

An expert panel convened in Chapel Hill, N.C. on June 9–10 by the National Toxicology Program (NTP) to review the scientific literature and

consider a recommendation by the North American Insulation Manufacturers Association to change the listing status for glass wool fibers in the upcoming 12th *Report on Carcinogens (RoC)*. ...[read more](#)



NIEHS-Funded Imaging Tool Logs 100,000th Job

The NIEHS-funded University of Cincinnati (UC) Center for Environmental Genetics (CEG) announced that its Bioinformatics

Core recorded its 100,000th job submission on June 11 for its popular POLYVIEW-3D imaging tool. ...[read more](#)



This Month in EHP

The July 1 issue of *Environmental Health Perspectives (EHP)* develops the theme “Climate Change Is Here,” with a Focus article on climate change abatement strategies and a Spheres of

Influence feature exploring the challenge of adapting to climate change already underway. ...[read more](#)



Wilcox to Speak at Science Café July 14

Science goes informal each month at Durham’s Broad Street Café, which will host a talk by NIEHS Senior Investigator and epidemiologist Allen

Wilcox, M.D., Ph.D.. ...[read more](#)

NIEHS Spotlight



Presentation Highlights MS and Workplace Issues

In a June 9 presentation viewed as a job-site videocast at NIEHS, two major advocacy groups for people with disabilities explored the topic “Multiple Sclerosis (MS) in the Workplace” and the anticipated impact of the new Americans with Disabilities Act Amendments Act (ADAAA) and new regulations yet to be issued.
[read more](#)



Trainees Vanpool with Mentor for ENDO 09

They weren't exactly Ken Kesey's Merry Pranksters, but members of the NIEHS Molecular Endocrinology Group had plenty of fun and bonding on their own road trip to ENDO 09 June 10–13 in Washington.
[read more](#)



NIEHS-Funded Leukemia Researcher Honored for Lifetime Achievement

University of California (UC), Berkeley epidemiologist Patricia Buffler, Ph.D., whose research NIEHS supports, was honored by the United Kingdom (U.K.)-based charity, CHILDREN with LEUKAEMIA June 24 for her lifetime contributions in the field of childhood leukemia research.
[read more](#)



Former NIEHS and EPA Toxicologist Kate Mahaffey Remembered

Friends and colleagues at NIEHS and elsewhere were saddened and shocked to learn of the sudden passing of former NIEHS scientist and policy specialist Kathryn (Kate) Mahaffey, Ph.D., on June 2 in Washington, D.C.
[read more](#)

Extramural Research

Extramural Update

The scientific statement “Endocrine Disrupting Chemicals: An Endocrine Society Scientific Statement,” which was announced at a news conference June 10 by Robert M. Carey, M.D., president of The Endocrine Society, and published in the journal *Endocrine Reviews*, marks an important step forward for research on endocrine disruption.
[read more](#)

Extramural Papers of the Month

- [Dioxins in Food Chain May Cause Poor Milk Production](#)
- [Genome-Wide Association Study Identifies Asthma Gene](#)
- [Glutathione S-Transferase Polymorphism Increases Risk of Second Primary Malignancy](#)
- [PCBs May Alter *in utero* Neonatal Brain Development](#)

Intramural Research

Intramural Papers of the Month

- [Anti-Hu is a Possible Marker for Small Cell Lung Cancer](#)
- [Environmental and Genetic Factors Are Basis of Disease](#)
- [Hyaluronan Contributes to Murine Airway Hyperresponsiveness](#)
- [Development of Polycystic Kidney Disease and Type I Diabetes in Glis3-Deficient Mice](#)

Inside the Institute



Program Celebrates Asian and Pacific Islander Heritage

NIEHS commemorated Asian/Pacific Islander Heritage Month on May 27 with a talk

on Oriental medicine in Rodbell Auditorium, followed by ethnic food sampling and a hula dance performance and instruction in the NIEHS cafeteria. [...read more](#)



Another Scorching Friends and Family Day

No one actually plans it that way, but NIEHS Friends and Family Day, which moved outdoors in 2007, always

seems to coincide with some of the hottest days of summer. [...read more](#)



Staff Mingle at Keystone's Beach Party

In a second major effort to give NIEHS staff in the Keystone Building a lunchtime opportunity to get to know their

neighbors better, volunteers from the three floors organized a beach-themed cookout on June 4. [....read more](#)



NIH-Hosted Panel Addresses GLBT Health Disparities

As part of its annual "Noons in June" series recognizing Gay, Lesbian, Bisexual and

Transgender (GBLT) Pride Month, NIH hosted a panel discussion on June 17 on "Addressing Health Disparities in GLBT Populations" at Lister Hill Auditorium on the NIH campus in Bethesda, Md. NIH made the presentations available for remote viewing via webcast. [....read more](#)

Calendar of Upcoming Events

- **July 1**, in Rodbell Auditorium, 11:00–12:00 — Summers of Discovery Seminar Series, "DNA Repair" with Thomas Kunkel, Ph.D.
- **July 6–10 (Offsite Event)**, at Lake Tahoe — [Green Technology Entrepreneurship Academy](#)
- **July 8**, in Rodbell Auditorium, 11:00–12:00 — Summers of Discovery Seminar Series, "Career Options in the Biomedical Sciences"
- **July 8 (Offsite Event)**, at the U.S. Capitol in Washington, 5:00–7:00 p.m. — Society of Toxicology Reception to Welcome Linda Birnbaum, Ph.D., as director of NIEHS and NTP, [registration](#) required
- **July 14 (Offsite Event)**, at the Broad Street Café in Durham, 7:00 p.m. — Allen Wilcox, M.D., Ph.D., discussing the key steps of human conception and early pregnancy
- **July 15**, in Rodbell Auditorium, 11:00–12:00 — Summers of Discovery Seminar Series with Dori Germolec, Ph.D., addressing "Allergic Disease — Immunology and Detection"
- **July 22**, in Rodbell Auditorium, 11:00–12:00 — Summers of Discovery Seminar Series, "Xenobiotic Metabolism and Transport" presented by David Miller, Ph.D.
- **July 23–24**, in Rodbell Auditorium, 8:30–5:00 — NTP Board of Scientific Counselors meeting
- **July 27**, in Rodbell Auditorium, 11:00–4:00 — NIEHS Clinical Research Unit Grand Opening — Welcoming Ceremony, Ribbon Cutting and Clinical Research Lectures
- **July 28**, in Rodbell Auditorium, 11:00–12:00 — Frontiers of Environmental Sciences Lecture Series, speaker and topic TBA
- **July 29**, in Rall Building, 8:00–5:00 — Summers of Discovery Annual Poster Session
- **July 29–30 (Offsite Event)**, at the Lowes Miami Beach Hotel - Miami Beach, 8:00–5:00 — PPTOXII - Role of Environmental Stressors in the Development of Origins of Disease
- View More Events: [NIEHS Public Calendar](#)

NIEHS Spotlight

NIEHS Sponsors New Jersey Town Hall Meeting

By Eddy Ball

NIEHS scientists traveled to New Brunswick, N.J., in support of a June 17 Environmental and Child Health Town Meeting that included opening comments by NIEHS and National Toxicology Program (NTP) Director [Linda Birnbaum, Ph.D.](#) The program was organized by the [NIEHS Center for Environmental Exposures and Disease \(CEED\)](#), which is housed in the Environmental and Occupational Health Sciences Institute (EOHSI) at the University of Medicine and Dentistry of New Jersey (UMDNJ). The meeting was held at the Jane Voorhees Zimmerli Art Museum on the Rutgers campus in New Brunswick.

The event was an opportunity for Birnbaum, a native of New Jersey, to visit the city where NIEHS held its first town hall meeting in 1998. She told her audience at the evening session of the program that NIEHS is proud of its “long history of seeking involvement from a broad array of constituencies, including scientists, health care professionals and communities, in setting its research agenda and in fostering community-university partnerships to implement parts of that agenda.”

“As we go forward, we want to make sure we are supporting the most important types of science, from ‘small science’ conducted by individual labs, which can be nimble and innovative, to ‘big science’ research teams, which may be needed to answer some of the most intractable questions,” Birnbaum explained. “We will need to use a judicious mix of the best individual investigators, as well as the capabilities of research teams, to uncover all the complex ways in which environmental exposures work on biological systems with genetic and other host susceptibility mechanisms to affect health and disease.”

An afternoon program of expert speakers opened with a welcome and introduction by UMDNJ Professor of Environmental and Occupational Medicine [Helmut Zarbl, Ph.D.](#), who is the principal investigator on the university’s NIEHS Center grant. Zarbl was followed by talks by UMDNJ investigators on findings of their NIEHS-funded research. The presenters included Michael Gochfeld, M.D., Ph.D., Jason Richardson, Ph.D., Michael Gallo, Ph.D., and Kathy Black, Ph.D. They spoke on such environmental health topics as heavy metal exposure, neurological disorders linked to pesticides, endocrine disruption and breast cancer and childhood asthma. A poster session and reception followed.



One of many high points at the Town Hall Meeting was the student panel discussion. Area middle school students, above, described what they’ve learned about environmental health through an NIEHS-funded outreach project. (Photo courtesy of Wilson Rodriguez and UMDNJ)



There were few empty chairs at either of the sessions, as students and people from the community turned out to hear experts and leaders in the environmental health sciences. (Photo courtesy of Wilson Rodriguez and UMDNJ)

The evening program opened with Birnbaum's comments and a brief panel session of local middle school students involved in the CEED Community Outreach and Education Program, leading into the highlight of the evening — a 90-minute panel session with scientists and environmental justice and public health advocates.

NIEHS Epidemiology Branch Staff Scientist [Jane Hoppin, Sc.D.](#), was one of the five members of the evening panel discussion. Hoppin described her research as part of the Agricultural Health Study and how “what we learn from farmers and their families [can be] relevant to the U.S. population as the chemicals used in agriculture are used for residential and public health purposes as well.”

Hoppin was joined by two UMDNJ professors — Daniel Wartenberg, Ph.D., and Robert Laumbach, M.D. — as well as Elyse Pivnick, vice president of [Environmental and Community Health](#) at the non-profit organization [Isles in Trenton, N.J.](#), and Ana Baptista, Ph.D., program manager of the [Ironbound Community Corporation](#) in Newark, N.J..



“We’re particularly glad to be back here now to focus our attention on children and environmental health,” Birnbaum said. (Photo courtesy of Wilson Rodriguez and UMDNJ)



As they mingled with attendees during the reception, it was evident that Birnbaum, center, and Hoppin, right, were in New Jersey to listen as well as speak. (Photo courtesy of Wilson Rodriguez and UMDNJ)

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While the NIEHS representatives were in New Brunswick, they visited faculty and staff of the NIEHS Center at UMDNJ. Standing, left to right, are Laura Hemminger, Mitchel Rosen, Junfeng (Jim) Zhang, Ph.D., Mark Robson, Ph.D., and Glenn Paulson, Ph.D. Seated, left to right, are Hoppin, NIEHS Associate Director Allen Dearry, Ph.D., Birnbaum and Audrey Gotsch, Dr.PH. (Photo courtesy of Audrey Gotsch and UMDNJ)

Superfund and EPA Host Combustion By-Products Congress

By Eddy Ball

A cross disciplinary group of scientists gathered June 1–3 at the U.S. Environmental Protection Agency (EPA) in Research Triangle Park, N.C. for the 11th International Congress on Combustion By-Products and Their Health Effects. The event was sponsored by the [NIEHS Superfund Research Program \(SRP\)](#), EPA, Louisiana State University (LSU), National Science Foundation (NSF), Electric Power Research Institute and Navistar.

Organized around the theme of “Combustion Engineering and Global Health in the 21st Century: Issues and Challenges,” the [meeting](#) brought together specialists in engineering, chemistry, biomedicine, toxicology and risk assessment, to interact and discuss recent developments and future goals in the control of combustion by-products and understanding of the effects of exposure on human and ecological health. Among the session speakers was 2006 NIEHS Outstanding New Environmental Scientists [awardee](#) and LSU Medical Center Assistant Professor [Stephania Cormier, Ph.D.](#) (see [related story](#)).

Representing the hosting agencies were NIEHS SRP Director William Suk, Ph.D., and U.S. EPA National Program Director of the Clean Air Research Program Dan Costa, Sci.D. They welcomed attendees and set the stage for plenary talks by John Bachmann, Ph.D., former EPA policy director and president of Vision Air Consulting, and [NIEHS grantee](#) Douglas Dockery, Sc.D., principal investigator on the breakthrough [Six Cities Study](#) and a professor in the Harvard University School of Public Health.

Bachmann, who spent most of his career at EPA in regulation, surveyed the highs and lows of federal air quality regulation in a talk titled “Hap-hazard: Regulation of Toxic Air Pollutants in the 20th and 21st Centuries.” He presented cost-benefit analyses to support his call for an integrated approach to regulation of particulate matter (PM) and pointed to “win-win” strategies such as a pilot diesel truck stop electrification project that demonstrated dramatic reductions in idling emissions while also reducing use of fuel.



Suk's opening remarks reflected the trend to combine climate and air quality studies in a cross-disciplinary global research agenda. He observed that “biomass fuel emissions affect two to three billion people worldwide and lead to more than 150,000 premature births each year,” as those same emissions contribute to climate change. (Photo courtesy of Steve McCaw)



Don Lucas, Ph.D., right, of the Lawrence Berkeley National Laboratory held the Adel Sarofim Award plaque (see [text box](#)) before presenting it to the group's Chair of the Executive Committee, [SRP grantee](#) Barry Dellinger, Ph.D. (Photo courtesy of Steve McCaw)



SRP Program Administrator Heather Henry, Ph.D., enjoyed a little comic relief during talks on the first day of the meeting. She introduced the second round of plenary speakers on June 2. (Photo courtesy of Steve McCaw)

Dockery reviewed some of the best-known air pollution disasters and his group's Six Cities epidemiology studies that began in 1974. He said the "evidence is overwhelming on the mortal effects of chronic exposure." He observed that, in initial and follow-up studies, "as PM 2.5 [micron] concentrations went up, we saw increased mortality." Dockery maintained that air quality regulations contributed significantly to the increased life expectancy reported in his 2009 *New England Journal of Medicine* [study](#).

In her talk the following day, EPA and NSF grantee **Kimberly Prather, Ph.D.**, a professor of chemistry at the University of California (UC), San Diego, described how she has adapted mass spectrometry to perform real-time "on-the-fly" single particle analysis for developing "fingerprints" for pinpointing the sources of air pollution. Observing that "aerosols contain thousands of organic species," she said that rather than trying to regulate individual species and metals, identifying and regulating the sources — autos, trucks, ship exhaust from nearby ports and biomass burning — may offer a better strategy for improving air quality.

Reporting on work supported by an [SRP grant](#), Ian Kennedy, Ph.D., a professor of engineering at UC, Davis, followed Prather with a talk on "Engineered Ultrafine Particles for Health Effects Studies." As **Kennedy** explained, nanoscale metal oxides constitute an important subclass of the PM emissions from combustion sources. His lab is pursuing studies of the relative toxicity of the different metals found in air, as well as identifying what variables affect the bioavailability of nanoscale particles.

Recognizing an Outstanding Scientist — Veteran Superfund Grantee Barry Dellinger, Ph.D.

On June 1, the 11th International Congress on Combustion By-Products and Their Health Effects honored one of its own, when LSU environmental chemist **Barry Dellinger, Ph.D.**, received the group's Adel Sarofim Award for Excellence in Combustion Research.

The award is named for chemical engineer and combustion research pioneer **Adel Sarofim, Ph.D.**, who is currently the Presidential Professor in the College of Engineering at the University of Utah. Work by the former Massachusetts Institute of Technology professor spanning more than 50 years has led to important advances in combustion science and reductions in the release of pollutants from fossil fuel combustion.

As presenter Don Lucas explained in presenting the award, "Barry and his colleagues studied how polychlorinated dioxins and furans are formed, including, and especially under, pyrolysis [high-temperature burning] and post-flame combustion conditions." Lucas also said Dellinger has helped to cultivate an "interface between biomedicine and engineering to determine the actual mechanism of biological activity, the source of [persistent, combustion-generated] radicals and their fate at atmospheric conditions."

As the many session presentations at the meeting bearing his imprint demonstrated, Dellinger is also an accomplished mentor and leader who is helping to shape the cross-disciplinary directions of transformational research in the field.

On June 3, Robert Devlin, Ph.D., chief of the Clinical Research Branch of the EPA Human Studies Division, gave the meeting's final plenary talk on continuing research needs, "Health Effects of PM: What Can We Learn from Toxicology Studies?" Devlin addressed the central paradox of air pollution health effects research — why some groups of people appear to have clinically significant adverse health effects from exposures, while others do not — and called for more research into understanding research into the biomolecular mechanisms of air pollution and subsequent health effects.



Dockery gestured as he related the success story of air quality regulation in Dublin, Ireland. After the Irish government banned the sale of coal there in 1990, PM emissions dropped by 70 percent and air pollution-related mortality declined across the board by seven percent. (Photo courtesy of Steve McCaw)



Abandoning his laser pointer, Bachmann favored a hands-on approach as he explained that "accidentally on-purpose [regulation] really worked" in the early years, although current and future challenges require a more systematic, integrated approach to risk assessment. (Photo courtesy of Steve McCaw)



Prather said her team matches readouts of mass spectrometry peaks from ambient air samples to a library of "fingerprints" to identify specific sources of air pollution and their respective contributions to total burden. (Photo courtesy of Steve McCaw)



Among the attendees were LSU Research Associate Lavrent Khachatryan, Ph.D., left, who participates in SRP-funded research efforts, and NIEHS Scientific Review Branch Science Review Administrator Sally Eckert-Tilotta, Ph.D. (Photo courtesy of Steve McCaw)



At the end of his talk, Kennedy joked about California's budget crisis. "I'll be happy to take questions," he quipped, "but, coming from the University of California, I'd be even happier to take donations." (Photo courtesy of Steve McCaw)

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Hrynkow Honored for Mentoring

By Eddy Ball

NIEHS Associate Director [Sharon Hrynkow](#) was one of two NIH women scientists honored by the Bethesda chapter of the Association for Women in Science (AWIS) with the organization's annual Award for Excellence in Mentoring. During the May 13 AWIS Mentoring Workshop at the Cloisters on the NIH campus in Bethesda, Md., AWIS board member Michelle Arnold, Ph.D., presented Hrynkow and Orna Cohen-Fix, Ph.D., with certificates of appreciation.

Arnold cited Hrynkow's efforts since 2000 on behalf of junior scientists, during her tenure as deputy director and acting director of the Fogarty International Center and in her current role as NIEHS associate director assigned to the Institute's office in Bethesda. Arnold pointed to [new programs](#) created by Hrynkow "to support and mentor scientists in resource-limited nations and novel approaches to supporting U.S. undergraduates and graduate students in global health." She also noted Hrynkow's keynote address on the important role of women in taking the lead to save the planet at this year's [NIH celebration of Women's History Month](#).

Hrynkow has been vocal in her support of women and young scientists in talks and programs at NIEHS as well. In 2008, she was the chair of the planning committee for the NIEHS Women's History Month celebration, which included a special International Women's Day [panel discussion](#) by NIEHS scientists and a series of invited lectures by outstanding women scientists. In December 2007, shortly after her appointment as an NIEHS associate director, Hrynkow gave a Frontiers of Environmental Sciences Lecture Series presentation titled "[A Conversation on Gender, Equity and Environmental Health](#)."

A principal investigator at the National Institute of Diabetes and Digestive and Kidney Diseases, [Cohen-Fix](#) is the co-director of the Johns Hopkins University/NIH Graduate Partnership Program and a past member of the Howard Hughes Medical Institute (HHMI)/NIH Research Scholars Program committee. She also served on the NIH Status of Intramural Women Scientists task force. Arnold praised Cohen-Fix for "her enthusiastic mentoring of the trainees in her laboratory" and her ability to balance "excellent research, editorial work and intramural NIH activities with a full family life."

Since the [Bethesda Chapter of AWIS](#) was formed in 1991, its membership has grown to more than 150 women in science. Its members are actively engaged in scientific research, education, administration and policy activities and are employed in federal agencies, academia, business and non-profit organizations. The chapter enjoys generous support from the NIH Office of Research on Women's Health, Office of Community Liaison and National Library of Medicine.

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Hrynkow chaired a planning meeting of international women scientists at NIEHS in February 2008. (Photo courtesy of Steve McCaw)



Cohen-Fix, left, posed with Arnold and the award certificate. Arnold is an investigator at the National Institute of Allergy and Infectious Diseases. (Photo courtesy of the Bethesda Chapter of AWIS)

NIEHS at Endocrine Society Meeting

By Robin Mackar

NIEHS continues its tradition of having an impressive presence at the Endocrine Society's Annual Meeting. Even before the official meeting kicked off in Washington June 10–12, Jerry Heindel, Ph.D., program administrator in the Division of Extramural Research and Training (DERT) was giving the keynote presentation and leading a discussion on the topic of government and public health protection at a June 9 pre-conference focusing on the current state of knowledge about endocrine disruptors.

The daylong forum, "[The 2nd Endocrine Society Forum on Endocrine Disruptors: Best Science for Risk Management and Policy](#)," sponsored by the American Thyroid Association, the Society for Toxicology and the Society for the Study of Reproduction offered approximately 200 attendees an opportunity to hear experts from around the world discuss the latest evidence on endocrine disrupting chemicals and their effects on human health. Heindel was especially pleased to have others join in as co-sponsors of the forum. "Having big international societies joining us in sponsoring this event is a major step forward for the field. Endocrine disrupting chemicals is no longer an obscure area of research, but one that all disciplines can embrace."

Heindel's presentation focused on the breadth of science now available on endocrine disrupting chemicals and the role that scientists, societies and organizations can play in making sure that science gets used to improve public health. "It's not enough to just conduct and support the science — we also have to make sure it is used," Heindel stated. Heindel discussed the progress being made in the field, especially in animal and *in vitro* studies, and provided examples that demonstrate the impact that endocrine disrupting chemicals are having on human disease. He called on scientists to provide data that is useful for policy decisions and clinical practice. On June 12, Heindel also led a presentation that highlighted endocrine disruptor research at NIEHS.

Heindel pointed out that that NIEHS was instrumental in supporting this second major forum focused on endocrine disruptors as it was with the first forum in 2005. R. Thomas Zoeller, Ph.D., from the University of Massachusetts Amherst, spearheaded this year's event with an NIEHS [conference grant](#).

Another watershed moment at the annual meeting came when the Endocrine Society unveiled its [first-ever scientific statement identifying endocrine-disrupting chemicals as a significant concern to public health](#) (see [related story](#)) The statement presents evidence on the health effects of endocrine-disrupting chemicals as well as recommendations for increasing understanding and raising awareness of these effects.



Heindel has taken a leading role in NIEHS efforts to promote research into endocrine disruptors and their health effects. (Photo courtesy of Steve McCaw)



Trainees at NIEHS and elsewhere have benefited from Schrader's experience in government, academia and the private sector. (Photo courtesy of Steve McCaw)

“Within this statement we also make a number of recommendations to increase understanding of the effects of endocrine disruptors,” said Robert M. Carey, M.D., president of The Endocrine Society. “The recommendations include enhancing basic and clinical research, and advocating involvement of individual and scientific society stakeholders in communicating and implementing changes in public policy and awareness.”

Others from NIEHS, including William Schrader, Ph.D. John Cidlowski, Ph.D., Kenneth Korach, Ph.D., and a number of fellows from the Division of Intramural Research, also participated in events at the [annual meeting](#) and were pleased with the attention endocrine disruptors are receiving from The Endocrine Society. Both Korach and Cidlowski are previous Edwin B. Astwood Award winners.

Schrader, who serves as NIEHS deputy scientific director overseeing postdoctoral training and career development at NIEHS, was in his element as he participated in the society’s annual Endocrine Trainee Day. The highly interactive sessions provided opportunities for 275 graduate students, postdoctoral fellows and clinical fellows to hear from people in the field about a variety of topics including career development opportunities. Schrader served as plenary speaker in the Basic Science Track — one of three concurrent program tracks offered to the attendees. Schrader also gave a talk on “Preparing for and Giving a Job Seminar” during the skills breakout session.

(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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Birnbaum Speaks at Green Chemistry and Engineering Conference

By Eddy Ball

NIEHS and National Toxicology Program (NTP) Director Linda Birnbaum, Ph.D., was one of four distinguished participants in a panel discussion, “Design Signals from Environmental Health Sciences: What Every Chemist Should Know,” June 24 in College Park, Md. The panel was part of the 13th Annual Green Chemistry and Engineering Conference held June 23–25 at the Marriott Inn and Conference Center in College Park — a public-private partnership effort organized by the [Green Chemistry Institute](#) of the American Chemical Society (ACS).

Joining fellow panelists Howard Frumkin, M.D., Dr.PH., Peter DeFur, Ph.D., and Jane Houlihan, Birnbaum brought a toxicologist’s perspective to the discussion of environmental health science and its relevance for chemists and engineers. Her audience included members of the green chemistry movement for environmental sustainability in the development of new products and processes.

While most of the [12 Principles of Green Chemistry](#) that inspire the movement relate directly to increasing safety and reducing



Birnbaum, above, urged her audience to bear in mind that “chemicals ‘live’ beyond their initial intended use.” (Photo courtesy of Mikal Ankrah - ACS Green Chemistry Institute®)

pollution, Birnbaum focused on one principle that has special resonance for environmental scientists and environmental public health advocates concerned with the persistence of dangerous chemicals in the environment — the principle of designing for degradation.

In her presentation on “Environmental Chemicals and Health,” Birnbaum reviewed basic concepts of research into the toxic effects of chemicals and discussed classes of chemicals with documented or suspected risk for adverse health effects — particularly those that persist in the environment beyond their initial intended use. She introduced the toxicological concepts of persistence, bioaccumulation, toxicity, “dose” and timing, as she addressed the classes of chemicals of special concern.



Seated from left to right was panelist Houlihan, vice president for Research at the Environmental Working Group; DeFur, president of Environmental Stewardship Concepts and affiliate associate professor in the Center for Environmental Studies at Virginia Commonwealth University; and Frumkin, director of the National Center for Environmental Health at the Agency for Toxic Substances and Disease Registry; and NIEHS and NTP director Birnbaum. (Photo courtesy of Mikal Ankrah - ACS Green Chemistry Institute®)

Birnbaum reviewed research supported by NIEHS, NTP and others on the health effects of a long list of chemicals that fall into the categories of endocrine disruptors, perfluorinated acids and brominated flame retardants. As if that list weren't daunting enough, she also addressed the potential health threats posed by mixtures and engineered nanoparticles, which are yet to be fully investigated and characterized. She used a dramatic slide with before and after photos of Ukrainian President Viktor Yushchenko, who was poisoned by dioxin, to underscore the threat that the banned chemical still holds for humans through its persistence in the environment.

The panel was organized by Lin Kaatz Chary, Ph.D., of the Great Lakes Green Chemistry Network, and moderated by Karen Peabody O'Brien, Ph.D., executive director of [Advancing Green Chemistry](#), which receives [funding](#) from the NIEHS Superfund Research Program.

Organizers promoted the [conference](#) as an opportunity for scientists, engineers and corporate leaders engaged in the business of sustainability to assess their progress toward the goals contained in the 2006 report, “Sustainability in the Chemical Industry: Grand Challenges and Research Needs.” The meeting was also designed to help participants identify research objectives that still need to be met.

Birnbaum's invitation to speak at the event is further evidence of the role NIEHS is playing in the green chemistry movement. In October 2008, the [NIEHS Worker Education and Training Program \(WETP\) Fall Awardee Meeting and Technical Workshop](#) featured a green chemistry and engineering session as part of its program on new opportunities in the green economy.

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NIEHS at WHO Conference on Children's Health

By Rebecca Wilson

NIEHS Superfund Research Program (SRP) Director William Suk, Ph.D., and SRP Program Administrator Claudia Thompson, Ph.D., were among 450 attendees including researchers, non-governmental organization (NGO) representatives and health ministers at the the third World Health Organization (WHO) International Conference on Children's Health and the Environment, held in Busan, Republic of Korea June 7–10. NIEHS National Advisory Environmental Health Sciences Council member Nsedu Witherspoon also attended, representing the Children's Environmental Health Network in Washington, DC.

In collaboration with WHO, NIEHS has long been a strong supporter of children's global environmental health. NIEHS has assisted with establishing partnerships among researchers and institutes and focusing support on collaborations between developing and developed countries. "The goal of these conferences," said Suk, "is to increase the health and well-being of children, primarily with regard to their environmental exposures."

Organized by WHO and hosted by the Korean Ministry of the Environment and Ministry of Health, Social Welfare and Family Planning, the [conference](#) was a forum for sharing information regarding the reduction of infant mortality and ensuring environmental sustainability. In addition to the primary meeting, a satellite workshop of the Korean Paediatric Society introduced Korean pediatricians to the need to monitor children's exposure to environmental pollutants. Representatives from the International Paediatric Association presented at the workshop.

The conference included several well-attended breakout sessions. A session addressing the health effects of nanotechnology featured presentations by Suk and Professor [Peter Sly, M.D.](#), of the University of Western Australia. A second session that generated a great deal of interest explored the effects of asbestos exposure in children. The conference culminated with the acceptance by all participants of the Busan Pledge, which reaffirmed the need for collaboration and cooperation among NGOs, governments, researchers and communities.

The first WHO/NIEHS-sponsored International Children's Environmental Health Conference, held in Bangkok in 2002, marked the beginning of an increased emphasis on children's health globally. As a result of this focus, WHO has designated several programs as Collaborating Centres for Research on Children's Environmental Health.



Suk, above, moderated a panel discussion at the conference's Asbestos Forum. He also made a presentation at the Plenary Session. (Photo courtesy of William Suk)



Conference attendees enjoyed entertainment by a chorus of Korean children in traditional dress. (Photo courtesy of William Suk)

The organization published declarations of support for children’s environmental health, which were signed by governments and scientific organizations, and advocated for a marked increase in research being conducted internationally.

NIEHS is a leader in children’s environmental health in the U.S. and has been funding research in this area for the past 15 years. In coordination with the U.S. Environmental Protection Agency, NIEHS supports a national network of [Centers for Children’s Environmental Health and Disease Prevention Research](#) established 1998. The NIEHS also is providing leadership for the National Children’s Study, which was implemented in 2007.

(Rebecca Wilson is an environmental health information specialist for MDB, Inc., a contractor for the NIEHS Superfund Research Program and Worker Education and Training Program.)

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Autism Research Network Launches Major New Study

By Eddy Ball

With financial support from NIEHS, three other NIH institutes and the private non-profit Autism Speaks, on June 9 a network of leading autism researchers from three regions across the country launched one of the largest research studies of its kind to investigate early risk factors for Autism Spectrum Disorders (ASD) during a phone-in press briefing. The study, known as the Early Autism Risk Longitudinal Investigation (EARLI) and led by NIEHS grantee and Drexel University Principal Investigator Craig Newschaffer, Ph.D., is one of eleven [NIH Autism Centers of Excellence \(ACE\)](#) projects nationwide.

The [Drexel University School of Public Health](#) in Philadelphia is the national coordinator of the EARLI Study network, which will follow an enriched-risk pregnancy cohort of up to 1,200 participants. The study is well equipped to look across time for biological and environmental markers for autism due to study’s enriched-risk study design, extensive bio-sampling, wide ranging data collection, three-year follow-up period and multidisciplinary team of expert investigators.

“No other study can more comprehensively explore the impacts and interplay of environmental factors and genetic predisposition in the cause of autism,” said [Newschaffer](#), chair of the Department of Epidemiology and Biostatistics at the Drexel University School of Public Health. “Our approach is based on assessing potential autism risk factors through all-inclusive data collection that begins when a mother of a child with autism learns she is pregnant and continues through the early life of the new baby.”

The local research sites for the study include Drexel University School of Public Health and Children’s Hospital of Philadelphia (CHOP), University of California at Davis [M.I.N.D. Institute](#),



Newschaffer is the principal investigator on a grant administered by NIEHS. “We are casting a very broad net to collect exposure and genetic information in real time,” he said of the strengths of working prospectively with a large enriched-risk cohort. (Photo courtesy of Drexel University)

an NIEHS grantee, Johns Hopkins Bloomberg School of Public Health and the Kennedy Krieger Institute, and the Kaiser Permanente Division of Research in Oakland, Calif.

“This study has unprecedented potential to help answer many of the questions families affected by autism face everyday, including questions about the genetic and environmental factors that contribute to autism,” said [Linda Birnbaum, Ph.D.](#), director of NIEHS and the National Toxicology Program. “The EARLI Study is a very comprehensive investigation geared towards identifying early signs of autism and understanding its earliest possible causes.”

Along with Newschaffer, participating in the telephone press briefing were epidemiologist [Lisa A. Croen, Ph.D.](#), Kaiser Permanente; Associate Professor [M. Daniele Fallin, Ph.D.](#), Johns Hopkins Bloomberg School of Public Health; Professor [Irva Hertz-Picciotto, Ph.D.](#), University of California, Davis School of Medicine; [National Institute of Mental Health \(NIMH\)](#) Director Thomas R. Insel, M.D.; [Autism Speaks](#) Chief Science Officer Geraldine Dawson, Ph.D.; and [Rebecca Landa, Ph.D.](#), of the Kennedy Krieger Institute Center for ASD and Related Disorders.



Birnbaum is NIEHS representative on the [U.S. Department of Health and Human Services Interagency Autism Coordinating Committee \(IACC\)](#). (Photo courtesy of Steve McCaw)

Networking for a Large-Scale Epidemiological Study of Gene-Environment Interactions

The Early Autism Risk Longitudinal Investigation (EARLI) Network promises to pull together several lines of research from earlier CHARGE investigations and explore new directions in a ten-year study of mothers of autistic children and their newborn siblings that combines epidemiology and basic laboratory research. The network includes an administrative center at the Drexel University School of Public Health, a data coordinating center at the University of California, Davis, a central lab and repository at Johns Hopkins School of Public Health, and field sites in Philadelphia, Baltimore, the San Francisco Bay area and Davis, Calif.

The network plans to implement a core epidemiologic data collection protocol focusing on prospective documentation of exogenous exposures, continuous ASD behavioral domains during pregnancy and early life, collection and banking of biological samples, and follow-up of the newborn siblings through 36 months of age. Researchers will gather data on ASD diagnoses, continuous ASD behavioral domains and other behaviors that may be associated with ASD.

Principal Investigator Craig J. Newschaffer, Ph.D., of Drexel University, listed four “exemplary specific aims” to be addressed in the study:

- Determine whether markers of maternal autoimmune status, measured during pregnancy, at delivery and at six months post-partum, are associated with autism risk
- Determine whether *in utero* exposure to persistent organic pollutants is associated with autism risk
- Explore maternal and child epigenetic marks as predictors of ASD risk
- Assess whether polymorphisms, which may affect brain development, and *in utero* agonist exposure are associated with autism risk and explore potential interaction of genotype and exposure
- Data collected in this large study are intended to serve as a resource for ongoing epidemiologic investigation of potential risk factors and risk biomarkers for ASD well into the future.

The EARLI Study is a public-private partnership supported by a \$14 million Autism Centers of Excellence grant awarded by the NIEHS, NIMH, [Eunice Kennedy Shriver National Institute of Child Health and Human Development \(NICHD\)](#) and [National Institute of Neurological Disorders and Stroke \(NINDS\)](#) and a \$2.5 million grant from Autism Speaks to the Drexel University School of Public Health.

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NIEHS Health Science Administrator Lawler, Ph.D., administers grants to EARLI and the M.I.N.D. Institute that are part of NIH support for the EARLI study. (Photo courtesy of Steve McCaw)

Institute Staff Supports Intramural Colleagues at Board Review

By Robin Mackar

Staff from throughout the Institute showed up to support their intramural colleagues June 15–16, as the NIEHS Epidemiology Branch and Fred Miller, M.D., Ph.D., presented their scientific findings and future plans during the Division of Intramural Research [Board of Scientific Counselors \(BSC\)](#) Review of the two programs.

The open session began Monday morning in Rodbell auditorium with some brief introductory remarks by BSC Chairman Jack Keene, Ph.D., followed by a welcome from NIEHS Director Linda Birnbaum, Ph.D. Birnbaum thanked NIEHS staff for supporting their colleagues and thanked the Board for its hard work in evaluating the programs.

Miller, chief of the [Environmental Autoimmunity Group](#), was the first investigator to present. He began by pointing out the uniqueness of his group, explaining that it is the only NIEHS scientific group in Bethesda and is housed in the NIH Clinical Center. He highlighted his work to define environmental and genetic risk and protective factors for systemic autoimmune diseases — especially muscle diseases known as myositis.

The second presentation was an overview of the [Epidemiology Branch](#) by Chief Dale Sandler, Ph.D. Sandler emphasized the prominent role that mentoring plays for the branch scientists and highlighted the fact that there has been a 35 percent increase in trainees in the Branch since 2005. Sandler also her work in two major efforts the NIEHS is involved in — the [Agricultural Health Study](#) and the [Sister Study](#).



Keene listened carefully as the investigators explained the rationale behind their respective study designs. (Photo courtesy of Steve McCaw)

Next, Walter Rogan, M.D., presented the work being done in the [Pediatric Epidemiology](#) arm of the branch. He focused predominantly on his work on soy formula and phytoestrogens. He noted that the lack of standard methods for evaluating estrogen effects in infants led him and his collaborators to develop the three cross-sectional pilot studies that were part of the [Study of Estrogen Activity and Development \(SEAD\) Soy Study](#).

The head of the [Aging and Neuroepidemiology Group](#), Honglei Chen, M.D., Ph.D., then discussed his work in the area neurodegenerative disease. He discussed two major collaborative projects — the [Parkinson’s, Genes & Environment \(PAGE\) study](#), which is underway, and the Shanghai Parkinson’s Study, scheduled to start soon.

Matthew P. Longnecker, M.D., Sc.D., highlighted his work as the lead in the [Biomarker-based Epidemiology Group](#), with an emphasis on his work on environmental contaminants such as DDT and organophosphate insecticides.

Allen Wilcox, M.D., Ph.D. rounded out the first full day with his work in the area of [reproductive epidemiology](#). He focused on his group’s important contributions to understanding the role that genetic susceptibility and environmental factors such as maternal smoking, folic acid supplements and alcohol might play as risk factors for facial clefts in infants.

The second day began with an excellent overview by Stephanie London, M.D., Dr.P.H. who highlighted two major areas that her group, the [Genetics, Environment and Respiratory Disease Group](#), focuses on — genetic susceptibility and early life exposures to respiratory and allergic diseases.

Donna Baird, Ph.D., who heads the Branch’s [Women’s Health Group](#) focused on her work on uterine fibroids, which affect more than 70 percent of women in the U.S. She discussed patterns of fibroid growth, as well as some of the risk factors associated with fibroids and possible preventive measures that may help prevent development of fibroids.

The final presentation was made by Jack Taylor, M.D., Ph.D., head of the [Molecular and Genetic Epidemiology Group](#), who focused on gene-environment interactions in cancer. He also highlighted his group’s methodological work, including the development of tools that will benefit the field of epidemiology and public health, by integrating complex data from genome-wide association studies and HapMap to better select gene variants for epidemiologic studies.



Sandler was joined by other investigators in her praise for the contributions of trainees in the Epidemiology Branch. (Photo courtesy of Steve McCaw)



NIEHS Acting Scientific Director John Pritchard, Ph.D., right, and Deputy Scientific Director Steve Akiyama, Ph.D., were seated with Keene and NIEHS leadership during the presentations. (Photo courtesy of Steve McCaw)

In addition to the formal presentations, more than two dozen posters were prepared and presented by staff scientists, research fellows, and pre-and post-doctoral trainees.

A written summary will be provided by the BSC within two months after the review.

(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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Surrounded by colleagues from throughout the Institute, Taylor, center, waited his turn at the podium. The public portion of the reviews gave NIEHS staffers an opportunity to learn more about the research in the Intramural program. (Photo courtesy of Steve McCaw)

Presentation Highlights MS and Workplace Issues

By Eddy Ball

In a June 9 presentation viewed as a job-site videocast at NIEHS, two major advocacy groups for people with disabilities explored the topic “Multiple Sclerosis (MS) in the Workplace” and the anticipated impact of the new Americans with Disabilities Act Amendments Act (ADAAA) and new regulations yet to be issued (see [story](#)). The event, which was sponsored by the NIEHS Disability Advocacy Committee (DAC) and the NIH Office of Equal Opportunity and Diversity Management (OEODM) attracted employees of NIEHS and neighboring U.S. Environmental Protection Agency (EPA).

Collaborating on the [presentation](#) were lead speaker Steve Nissen, of the [National Capital Chapter of the National Multiple Sclerosis Society \(NMSS\)](#) in Washington, D.C., and U.S. Department of Labor [Job Accommodation Network \(JAN\)](#) consultants Beth Loy, Ph.D., and Melanie Whetzel. Representing NIEHS at the event were DAC chair Alicia Moore and EEO Specialist Gerard Roman.

The first part of the program was an overview of MS by Nissen, who is the national chapter’s director of Employment Programs and of Operation Job Match. He explained that MS literally means the “many scars” on myelin that result from “inflammatory attacks at multiple sites in the central nervous system.” He emphasized that the “hallmark of MS is its unpredictability and variability,” the kind of disability new provisions in the ADAAA are meant to address.



As Nissen, above, explained, “Approximately 60 percent of people with MS are working at the time of diagnosis, [but] several years down the road, the percentage remaining in the workplace drops to around 40 percent.” (Photo courtesy of the National Multiple Sclerosis Society)

“No two people with MS are the same,” Nissan observed as he described the broad range of visible and invisible challenges that the estimated 400,000 people with MS in the U.S. may experience in the workplace. Their symptoms range from overt movement and speech disabilities to “hidden” problems with fatigue, cognitive and emotional changes, pain, and systemic dysfunction.

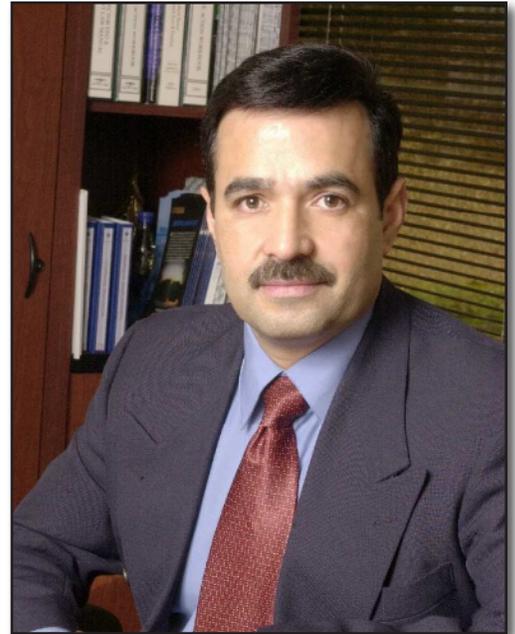
Diagnosed typically in the prime working years of age 20 to 50, it is more frequently seen in Caucasians and two to three times more common in women than men. Although there are some treatments, MS is incurable, and the condition is further complicated by an inexplicable pattern of remission and recurrence.

Because people with the condition need varying degrees of accommodation or even no accommodation at all, Nissen continued, the issue of disclosure can be problematic. Nissen, Loy and Whetzel each contributed their perspectives on how people with hidden and recurrent disabilities may want to approach the task of telling others of their needs for accommodation. Although legally the situation should become clearer as legal and regulatory interpretations of the ADAAA appear, disclosure still presents emotional challenges for workers with MS.

Throughout the presentation, Nissen, Loy and Whetzel emphasized that accommodation can be a win-win situation for workers and employers — as long as they approach their negotiations in a cooperative way. The ADAAA, Loy noted, is itself the result of “a cooperative effort between the business sector and the disability community,” with both groups supporting the extension of the law’s protection to more employees in a collaboration that promises advances toward the goal of equal opportunity employment.

As she listed several examples of accommodations, Loy said, “A lot of these things are about good management” and create no real burden for employers who can continue to benefit from the talents of employees with long-term or intermittent limitations. The presenters encouraged the audience to take advantage of the many resources for employees and employers available from [NMSS](#) and [JAN](#), as well as the comprehensive “[The 411 on Disability Disclosure](#)” workbook available at no cost. They also invited individuals to contact the organizations for more information and personalized consultation.

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Roman, above, is an NIH EEO specialist headquartered at NIEHS, and he is well versed in the extended coverage of the ADAAA and resources for people with disabilities. (Photo courtesy of Steve McCaw)



Moore, above, has become an expert on resources for accommodation. She and her fellow DAC members have extended an open invitation to employees at EPA to attend NIEHS presentations on the topic. (Photo courtesy of Steve McCaw)

Trainees Vanpool with Mentor for ENDO 09

By Eddy Ball

They weren't exactly Ken Kesey's Merry Pranksters, but members of the NIEHS [Molecular Endocrinology Group](#) had plenty of fun and bonding on their own road trip to ENDO 09 June 10–13 in Washington. With group head and Principal Investigator John Cidlowski, Ph.D., at the wheel, the five trainees dealt with a tight travel budget this year by taking an NIEHS van to the conference and doubling up in less expensive hotels in Washington.

The [annual meeting](#) of the Endocrine Society, ENDO, is one of the premier events each year for scientists involved in endocrine research, and each of the trainees had entered a study in the society's Presidential Poster Competition. In addition to Cidlowski, the group included Presidential Award-winner Danielle Duma, Ph.D., Erica Lannan, Ph.D., Rongqin Ren, Ph.D., Javier Revollo, Ph.D., and Lindsay Smith. For all except Duma, the trip was the first time the trainees had attended an ENDO meeting.

ENDO attracts as many as 7,500 scientists and practitioners each year, to hone their skills and share new research. Being honored by the Endocrine Society, as Cidlowski was [last year](#), can be a high point in an investigator's career and, for trainees, recognition at ENDO can help a CV stand out in the job search. The poster sessions also offer an especially good opportunity for networking and interacting with other scientists — and possible employers — with similar research interests.

Duma was the NIEHS fellow in the group who took home a Presidential Award, and all the trainees described the trip as a success, both professionally and as a way to get to know each other and their mentor better. "I thought it was interesting at the meeting," said Predoctoral Fellow Lindsay Smith, "that people came to see our projects because they had John's name on them as well."

Revollo added that "it was interesting for me to get to know John from a different angle," a feeling that Cidlowski also expressed about his trainees. "It was a great team-building experience," Cidlowski observed. "I learned a lot about each of them that I didn't even know from working with them on a daily basis."

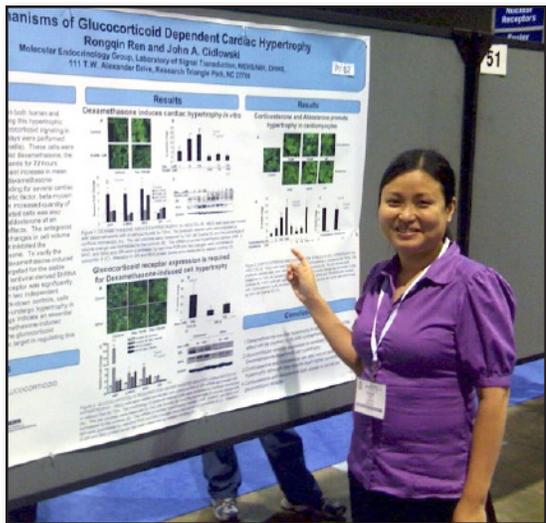
"The drive was easy," Cidlowski noted. "We had two people with GPS [Global Positioning Systems], and they guided us through the city from hotel to hotel. I think it took us only about an hour more than it would have if we'd taken a flight — and by the time you figure in getting a cab to the hotel, it was probably a wash."



Smith, left, and Duma clowned in the middle seats as the van made its way north on Interstate 95. Ren, in the background, rode shotgun for much of the trip. (Photo courtesy of Danielle Duma)



Revollo, left, and Lannan obviously enjoyed their time on the road with their colleagues. (Photo courtesy of Danielle Duma)



On the floor at ENDO, Ren showed off her research for other scientists at the meeting. (Photo courtesy of Danielle Duma)



Back at NIEHS, the travelers posed with their van. Standing, left to right, in the back row are Cidlowski, Duma and Lannan. In the foreground, left to right, Revollo kneels next to Ren and Smith. (Photo courtesy of Steve McCaw)

Danielle Duma's Award-Winning Abstract

Duma D, Collins JB, Chou JW, Cidlowski JA. Sexual dimorphism of glucocorticoids regulated rat liver gene expression.

Males and females exhibit differences in the incidence of many major diseases including autoimmune diseases, hepatocellular carcinoma, diabetes and osteoporosis, which all have important inflammatory components in their etiology. Glucocorticoids (GCs) are the primary physiological anti-inflammatory hormone in all mammals, and synthetic derivatives of these hormones are widely prescribed as anti-inflammatory agents, irrespective of gender. We wished to determine if differential sensitivity between males and females has a role in the sexual dimorphism of inflammation.

Microarray analyses were performed on livers from adrenalectomized male and female Sprague-Dawley rats untreated and treated with Dexamethasone (Dex) for 6 hours. The comparison between untreated and Dex-treated males and/or females reveals 6329 genes Dex regulated in males and 8234 genes Dex regulated in females. We applied computational analyses to the biological data set mentioned above using a profile-based method for **Extracting** microarray gene expression **Patterns** and **Identifying** co-expressed **Genes** (EPIG). Our data identify eight clusters of GC-regulated genes, grouped in four distinct patterns. Pattern 1 shows 3494 probe sets that are commonly regulated by GC in males and females. Pattern 2 shows 786 probe sets that are preferentially regulated by GC in females. Pattern 3 shows 1130 probe sets where the magnitude of response is higher in males. Interestingly, Pattern 4 identified an unexpected profile of gene expression: 199 probe sets GC responsive in both sexes but regulated in opposite directions. In addition, pathways analysis was applied to the data set identifying sex-specific glucocorticoid regulated gene expression in several canonical pathways that have been implicated in human disease, in which disease susceptibility is sex-biased. For example, a comparison of the number of genes involved in inflammatory disorders between sexes revealed 84 additional GC-responsive genes in the male rat.

Taken together, our data suggest that GCs through sexually-dimorphic regulation of gene expression modulate gender-specific homeostatic functions in male and female liver and raises the possibility that the anti-inflammatory effect of GCs maybe more dramatic in males than females and may explain why females have a higher risk of develop auto-immune diseases than do males.

NIEHS-Funded Leukemia Researcher Honored for Lifetime Achievement

By Colleen Chandler

University of California (UC), Berkeley epidemiologist Patricia Buffler, Ph.D., whose research NIEHS supports, was honored by the United Kingdom (U.K.)-based charity, CHILDREN with LEUKAEMIA June 24 for her lifetime contributions in the field of childhood leukemia research. The award was one of four bestowed at the organization’s annual awards ceremony, “Celebrating Science: Current Successes, Future Hopes for Childhood Cancer.”

“Dr. Buffler was selected for this award in recognition of her life-long dedication to finding causes of childhood leukaemia and other childhood cancers, and her expertise in childhood cancer research, both nationally and internationally,” stated the organization’s announcement.

The CHILDREN with LEUKAEMIA 2009 Awards were presented at a reception in the Terrace Pavilion at the House of Lords in London, according to an organization spokesperson.

Leukemia is the most common form of childhood cancer in both the U.K and the U.S. The American Cancer Society estimates that more than 2,200 new cases are diagnosed each year. According to CHILDREN with LEUKAEMIA, there are an estimated 475 to 500 new cases each year in the U.K.

Buffler is a professor of epidemiology and dean emerita appointed as a Kenneth and Marjorie Kaiser Endowed Chair at UC Berkeley. She heads the Northern California Childhood Leukemia Study (NCCLS), a gold mine of data on environmental factors associated with childhood leukemia. She is also a member of the Institute of Medicine.

Besides NIEHS funding, Buffler receives funding from NCI and CHILDREN with LEUKAEMIA. Her work continues to build on the framework established with the epidemiological evaluation of data from 35 northern and central California counties under the NCCLS, resulting in a number of publications analyzing and expanding that data.



NIEHS grantee Patricia Buffler is shown at the award ceremony at the House of Lords in London. (Photo courtesy of Colin Hampden-White and CHILDREN with LEUKAEMIA)



The awardees posed beside the Thames on the terrace at the House of Lords. Shown, from left, were Anjali Shah, Ph.D., Caroline Blakey, acting chief executive of CHILDREN with LEUKAEMIA, Buffler, Frederick Langevin, receiving the award for K.J. Patel, Ph.D., and Nicholas Goulden, M.D. (Photo courtesy of Colin Hampden-White and CHILDREN with LEUKAEMIA)

“The NCCLS is an ongoing comprehensive molecular epidemiology study, which pioneered the use of a multidisciplinary approach to study molecular, toxicologic, genetic, environmental and epidemiologic factors related to the development of childhood leukaemia, and is one of the leading studies worldwide,” the CHILDREN with LEUKAEMIA award announcement said.

(Colleen Chandler is a writer/editor in the NIEHS Office of Communications and Public Liaison and a regular contributor to the *Environmental Factor*.)

Award-Winning Research on Childhood Leukemia

Buffler’s research is primarily focused on identifying gene and environment interactions related to leukemia. She and fellow researchers at Berkeley have looked at the following factors and their contributions to the development of childhood leukemia:

- How genes modify a child’s susceptibility to environmental exposures
- The *in utero* changes that initiate disease development
- The different molecular subtypes of leukemia and possible or likely associations with specific environmental exposures
- The link between household pesticides and an increased risk of developing leukemia
- The correlation between timing of exposure to pest controls and the associated risk, showing that exposure during pregnancy resulted in the highest risk
- The increased risk of exposure to professional pest control products and the development of the disease in childhood
- The effect of and timing of one or both parents’ smoking habits and their offspring’s chances of developing the disease
- The link between disease development and maternal diet
- The preventive effect of prenatal folate supplements as well as the detrimental effect of maternal alcohol consumption, which depletes folate bioavailability
- The possible effects of childhood diet and disease development
- The reduced risk associated with breastfeeding
- A possible association between childhood infections and leukemia.

Recent funding application information indicates that Buffler intends to widen the scope of the data collection and analysis to include information from Canada, the UK, France and Australia through the creation of international consortiums to look at the disease from a worldwide perspective.

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Former NIEHS and EPA Toxicologist Kate Mahaffey Remembered

By Eddy Ball

Friends and colleagues at NIEHS and elsewhere were saddened and shocked to learn of the sudden passing of former NIEHS scientist and policy specialist Kathryn (Kate) Mahaffey, Ph.D., on June 2 in Washington, D.C. She was 65 at the time of her death and is survived by her mother, husband, David Jacobs, four children and step-children, Two sisters and two grandchildren.

“NIEHS and the entire environmental community have lost a scientific leader, a spokesperson, and a friend,” said long term colleague, NIEHS and National Toxicology Program Director Linda Birnbaum, Ph.D. “I am personally saddened by the untimely passing of Kate as I was honored to work with her here at NIEHS, during our shared time at the EPA [U.S. Environmental Protection Agency] and since her retirement.”

Mahaffey worked in the NIEHS Office of the Director toward the end of the tenure of former Director David Rall, M.D., Ph.D., and early in the term of former Director Ken Olden, Ph.D., who assumed leadership of the Institute in 1991. She worked out of an office in Cincinnati, traveling regularly between her home and RTP.

An EPA official from 1993 to 2008, advisor to the World Health Organization and member of the National Academy of Sciences, Mahaffey was the primary author of the eight-volume EPA *Mercury Study Report to Congress* presented in 1998. She is credited with helping to make certain that children’s blood samples were analyzed for lead and included in the National Health and Nutrition Examination Survey run by the Centers for Disease Control and Prevention.

She started her federal career in 1972 as a project manager for lead contamination in foods at the U.S. Food and Drug Administration in Bethesda, Md., and later worked for the National Institute for Occupational Safety and Health in Cincinnati. Mahaffey had been a professor of toxicology at George Washington University School of Public Health and Health Services since August 2008 and was also working on the National Children’s Study. She mentored many scientists beginning their careers and tutored young children in math at a Washington elementary school.

In 2006, she received the Society of Toxicology’s Arnold J. Lehman Award for regulatory toxicology and risk assessment. In 2007, Mahaffey received the Bronze Medal for Commendable Service from the EPA for her work with mercury.

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After friends and colleagues learned of her death, tributes quickly began to appear online. (Photo courtesy of David Jacobs)

Science Notebook

Nuclear Compartmentalization Affects Gene Activity

By Robin Arnette

According to Harinder Singh, Ph.D., the NIEHS Distinguished Lecturer for June, the mammalian immune system protects the body from a plethora of microscopic invaders, and is also an excellent model for examining fundamental questions in molecular, cell and developmental biology. Over the years Singh has focused on how transcription factors that bind specific DNA sequences regulate the development of innate and adaptive cells of the immune system. On June 9, with Laboratory of Molecular Carcinogenesis Principal Investigator Paul Wade, Ph.D., lecture host, Singh presented “Gene Regulatory Networks Orchestrating Innate and Adaptive Immune Cell Fates.”

Singh divided his talk into two parts, with the first half dealing with the molecular mechanisms that underlie cell fate determination. He devoted the second portion of his seminar to a recent topic that was of interest to many in the audience — the issue of nuclear structure and the compartmentalization of the genome. “In other words,” he explained, “is the positioning of genes within the three-dimensional structure of the nucleus important in terms of all of the different DNA transactions, such as transcription, recombination and replication, which have to occur?”

Singh entered this area of research after studying B and T cells, the adaptive cells of the immune system, and their ability to generate large repertoires of antigen receptors through somatic DNA recombination. The protein that performs the recombination events for both cell types is called the V(D)J recombinase, but Singh wondered why the recombinase didn’t inappropriately recombine T cell receptor segments in developing B cells and vice versa. He said much of the data on the subject suggested that developmentally-regulated localized changes in chromatin structure controlled the enzyme’s accessibility to its substrates. He continued, “However, there may be additional processes, such as nuclear compartmentalization, that are used to restrict access of the recombinase to one set of receptor loci in a given lineage and not the other.”



Singh is the Louis Block Professor in the Department of Molecular Genetics and Cell Biology and chairman of the Committee on Immunology at the University of Chicago. He is also a member of the Cancer Research Center at the University and an Investigator at the Howard Hughes Medical Institute. (Photo courtesy of Steve McCaw)



Wade, above, watched the lecture slides from the shadows as Singh talked. When the lights came up afterwards, he fielded questions about the talk. (Photo courtesy of Steve McCaw)

Singh's group followed the positioning of these antigen receptor loci during lymphocyte development and revealed that immunoglobulin genes have a default position in which both alleles are initially positioned at the nuclear lamina just underneath the inner nuclear membrane in multipotential progenitor cells. During early B cell development, these alleles move away from this compartment and undergo transcriptional activation and DNA recombination. In the T cell lineage, immunoglobulin alleles remain associated with the nuclear lamina and do not undergo recombination.

To add to the mystery, other researchers in the field had reported that genes located at the lamina or the inner nuclear membrane were inactive, while those positioned away from the compartment were active. "We therefore decided to take an active gene that resides in the nucleoplasm and attach it to the inner nuclear membrane," Singh added. "We could then examine the consequences of relocalization on its activity."

Singh engineered murine fibroblast cells to carry the hygromycin gene with a herpes virus promoter and lac operators positioned downstream. He expressed the fusion protein emerin-GFP-lacI, which was targeted to the inner nuclear membrane through emerin, an inner nuclear membrane protein. IPTG withdrawal allowed the lacI domain to bind to the operators in the hygromycin gene. The experiment worked. The hygromycin gene and several nearby chromosomal genes were repositioned into the membrane compartment and underwent repression.

Singh pointed out that this kind of radical reconfiguration of individual chromosomes occurred after the cell went through one mitotic cycle, since this was the time when the chromosomes condensed and the nuclear envelope and lamina broke down. "That's when we think you get an opportunity to decide whether a gene in a given chromosome will be attached or not to this compartment in the new nuclei that are formed," he concluded.

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Daniel Menendez, Ph.D., a visiting fellow in the Laboratory of Molecular Genetics, enjoyed Singh's presentation and thought that the research was a particularly intriguing topic. "His talk made me realize how coordinated all of the processes that are occurring in the nucleus need to be," he said. (Photo courtesy of Steve McCaw)



NIEHS Molecular and Cellular Biology Group Visiting Fellow Zhong Jing Wang, Ph.D., above, described Singh's presentation as "very instructive, refreshing and mind-opening" with its "comprehensive novel research concepts and strategies." (Photo courtesy of Steve McCaw)

Jordt Extends ONES Research on TRPA1 in Study on Asthma

By Eddy Ball

Leading a 15-person team of researchers, NIEHS Outstanding New Environmental Scientist (ONES) [awardee](#) Sven-Eric Jordt, Ph.D., reported new findings on the role of sensory neuronal ion channel activation in producing airway inflammation and hyperactivity in asthma. It is the latest report from Jordt's lab on experiments with two sensory transient receptor potential channels, TRPA1 and TRPV1, showing the potential for developing new interventions for the prevention and treatment of human disease and trauma. Funded in part by NIEHS, the [study](#) appears in the June issue of the *Proceedings of the National Academy of Sciences (PNAS)*.

Through a process of elimination, [Jordt](#), first author [Anabel Caceres, Ph.D.](#), and colleagues from the Department of Pharmacology, Department of Pathology and the Section of Pulmonary and Critical Care Medicine at Yale University School of Medicine established the critical role of TRPA1 — the mustard oil and acrolein receptor — in asthma and the efficacy of treatment with a TRPA1 antagonist known as HC-030031. The researchers also clearly showed that TRPV1, the capsaicin receptor, is not required for allergic airway inflammation in the OVA mouse model of asthma, despite its clear involvement in other symptomatic consequences of airway inflammation, such as chronic cough.

In their experiments, the team treated wild type, *Trpa1*-deficient and *Trpv1*-deficient mice with ovalbumin (OVA), which induces a Th2-directed allergic response, and HC-030031 — progressively establishing three lines of support for their hypothesis:

- *Trpa1*^{-/-} mice showed a marked reduction in mucus production and T_H2 cytokine levels in bronchoalveolar lavage fluid (BALF) following OVA challenge, as opposed to the robust induction in wild type and *Trpv1*^{-/-} mice with intact TRPA1 function.
- TRPA1 antagonist reduced airway inflammation and hyperreactivity when administered to wild-type mice during OVA airway challenge, resulting in diminished levels of T_H2 cytokines in BALF and much lower densities of inflammatory cells in histological sections of airways.
- A strong TRPA1 agonist, 2-chloroacetophenone (CN), produced marked increases in levels of neuropeptides in wild-type mice, but not in *Trpa1*^{-/-} mice, while pre-treatment with HC-030031 suppressed acute CN-induced neuropeptide release in airways.

In their discussion, the authors wrote, “The data in our present study support the idea that TRPA1 may function as an integrator of chemical and immunological stimuli modulating inflammation in the airways.” Moreover, they concluded, “Our study opens an avenue for asthma pharmacology, revealing TRPA1 as potential target for anti-asthmatic drugs,” and called for studies in additional animal models of asthma and other allergic inflammatory conditions.



Jordt, shown during his 2006 visit to NIEHS, is the first NIEHS extramural grantee (see [story](#)) to receive one of the prestigious Presidential Early Career Awards for Scientists and Engineers. (Photo courtesy of Steve McCaw)

From Basic Research to Public Health Applications

When Jordt visited NIEHS in 2006 to present his ONES research, he had already established that TRP channel receptors are part of an early warning system of sensory neurons during injury and chronic painful conditions triggering tears, sneezing, neurogenic inflammation, pain and respiratory constriction in the upper airways. He had also sufficiently characterized the basic thermo- and chemo-sensory mechanisms of TRPA1 and TRPV1 to hypothesize that blocking one or both of them might benefit people with asthma and people exposed to noxious agents, temperature extremes and environmental toxicants with irritant activities.

That basic research culminated in a May 2008 *Journal of Clinical Investigation* [study](#) using a mouse knockout strategy to demonstrate a crucial role of TRPA1 in detection of airway irritants, including chlorine and hydrogen peroxide. In their tests of respiratory function, Trpa1(-/-) mice displayed profound deficiencies in hypochlorite- and hydrogen peroxide-induced respiratory depression as well as decreased oxidant-induced pain behavior — demonstrating *in vivo* that TRPA1 is an oxidant sensor in sensory neurons, initiating neuronal excitation and subsequent physiological responses

The study led to a [paper](#) published in the April 2009 issue of *FASEB* linking the earlier findings to potential clinical applications. In those experiments, Jordt and colleagues in the Yale University Department of Pharmacology and Section of Pulmonary and Critical Care Medicine established a role for TRPA1 in the noxious effects of tear gases and toxic industrial isocyanates — the best known of which is the chemical released during the environmental disaster in Bhopal, India. The researchers also demonstrated that TRPA1 antagonists reduce the adverse health effects of exposures to a wide range of toxic noxious chemicals.

Because many of the environmental irritants activating TRPA1 are suspected of causing or exacerbating asthma, such as chlorine, aldehydes and cigarette smoke constituents, these studies, both featuring Postdoctoral Fellow [Bret Bessac, Ph.D.](#), as first author, helped lay the foundation for their latest findings about airway inflammation and hyperreactivity in knockout mice.

Citations:

[Bessac BF, Sivula M, von Hehn CA, Caceres AI, Escalera J, Jordt SE.](#) 2009. Transient receptor potential ankyrin 1 antagonists block the noxious effects of toxic industrial isocyanates and tear gases. *FASEB J* 23(4):1102-1114.

[Bessac BF, Sivula M, von Hehn CA, Escalera J, Cohn L, Jordt SE.](#) 2008. TRPA1 is a major oxidant sensor in murine airway sensory neurons. *J Clin Invest* 118(5):1899-1910.

Citation: [Caceres AI, Brackmann M, Elia MD, Bessac BF, del Camino D, D'Amours M, Witek JS, Fanger CM, Chong JA, Hayward NJ, Homer RJ, Cohn L, Huang X, Moran MM, Jordt SE.](#) 2009. A sensory neuronal ion channel essential for airway inflammation and hyperreactivity in asthma. *Proc Natl Acad Sci U S A.* 106(22):9099-9104. Epub 2009 May 19.

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New Study Links Intestinal Inflammation to Systemic Genotoxicity

By Laura Hall

Researchers at the University of California, Los Angeles (UCLA) have shown for the first time that intestinal inflammation is linked to systemic DNA damage in mice, and they speculate that indications of DNA genotoxicity could provide a non-invasive way to diagnose inflammatory bowel disease (IBD) in its earliest stages.

According to the researchers, DNA damage from ongoing bowel inflammation can lead to dysplasia and develop into cancer. The [study](#), which was partially funded by [NIEHS](#), appeared in the June 1 issue of *Cancer Research*.

Senior author [Robert Schiestl, Ph.D.](#), a UCLA professor of pathology, radiation oncology and environmental health sciences, said that detecting and treating inflammation early may prevent some abdominal, liver and colorectal cancers, as well as some lymphomas that have been linked to inflammatory diseases. DNA damage may be the “earliest detectable indicator” of intestinal inflammatory disease, explained [Jonathan Braun, M.D., Ph.D.](#), a co-author of the study and a professor and chairman of the Department of Pathology and Laboratory Medicine at UCLA.

IBD is an immune-mediated chronic inflammatory disease involving the mucosal cells of the intestinal wall. It includes ulcerative colitis (UC) and Crohn’s Disease (CD) and affects an estimated 3.6 million people in the U.S. and Europe. IBD runs in families with multiple clinical subgroups within both UC and CD. Several predisposing genes on multiple chromosomes have been identified. Nevertheless, genetics and environmental factors appear to be about equally responsible for the disease, which significantly increases risk of colorectal cancer and leads to greater risk of developing other cancers such as hepatobiliary carcinoma and hematopoietic cancers.

The study reports a link between bowel inflammation and DNA damage in tissues of the body far from the inflammation site. The researchers induced acute and chronic colitis using several mouse models that enabled them to parallel the symptoms and disease progression of human IBD. Schiestl and coauthors were able to compare bowel inflammation caused by an environmental agent, dextran sulfate sodium (DSS), to inflammation that occurs from genetic factors in knockout mice whose genetic makeup predisposes the animals to bowel inflammation.

Inhibitory cytokines suppress inflammation in the mucosal cells lining the gut. Proinflammatory cytokines are secreted to help destroy invading or damaged cells but, if uncontrolled, can lead to damage in what was healthy tissue. To measure the inflammatory effect of DSS, the researchers assayed for the messenger RNA expression of proinflammatory cytokines, as well as an anti-inflammatory cytokine in peripheral blood. The pattern of cytokine gene expression of chronically DSS treated mice mimicked that seen in IBD.

In contrast to other investigators who looked for damage close to the site of inflammation, the authors assayed for single and double-strand DNA breaks, oxidative DNA damage and cytogenetic damage such as chromosome breaks or abnormal chromosomes in peripheral blood. They found that “systemic genotoxicity is a prevalent feature of subclinical, acute, and chronic colitis.”



During an interview at UCLA, senior author Schiestl explained the significance of the study. “This was not known before — that intestinal inflammation causes damage that can be found throughout the body.” (Photo courtesy of UCLA)

Greater inflammation was associated with greater DNA damage in the blood, noted first author, Aya Westbrook, a graduate student at the UCLA Molecular Toxicology Interdepartmental Program. In addition, detectable DNA damage in blood cells at higher levels than in control animals could be seen even in treated animals that had mild inflammation without symptoms.

The results of this study show that DNA genotoxicity in peripheral blood cells has the potential to act as a biomarker of bowel inflammation, allowing a non-invasive way to test for IBD even at subclinical levels of the disease. “This may give us the opportunity to ward off the disease early and avoid the subsequent organ damage” and the development of cancer, Braun said. He added, “At present, the only way to diagnose the patients is to do full endoscopic examinations, which are both invasive and expensive.”

UCLA researchers have initiated a clinical trial to test these findings in humans.

Citation: Westbrook AM, Wei B, Braun J, and Schiestl RH. 2009. Intestinal mucosal inflammation leads to systemic genotoxicity in mice. *Cancer Res* 69 (11): 4827-4834.

(Laura Hall is a biologist in the NIEHS Laboratory of Pharmacology.)

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First author Aya Westbrook is a graduate student pursuing her doctorate in the UCLA Molecular Toxicology Interdepartmental Program at UCLA. She is currently working on her second paper as first author. (Photo courtesy of Aya Westbrook)

LSU ONES Awardee Links Protein Misfolding to Ultrafine PM

By Eddy Ball

On June 2, [NIEHS grantee](#) Stephania Cormier, Ph.D., spoke as part of the Organics and Free Radicals Session of the 11th International Congress on Combustion By-Products and Their Health Effects at the Environmental Protection Agency conference center in Research Triangle Park, N.C. (see [related Spotlight story](#)). Cormier presented the latest data from her studies on differential protein expression and post-translational modification in lung tissue of rodent neonates exposed to surrogate combustion-generated ultrafine particulate matter (PM) with persistent free radicals and the link to increased risk for adult-onset inflammatory lung disease.

[Cormier](#) is an assistant professor of pharmacology at the Louisiana State University School of Medicine in New Orleans and a 2006 NIEHS Outstanding New Environmental Scientist [awardee](#). She is investigating the gene-environment interactions triggered by air pollution PM measuring 0.1 microns or less in diameter.

Her group is particularly interested in the role of ultrafine PM in the predisposition to adult airway inflammatory disease, such as chronic obstructive pulmonary disease (COPD) and asthma, resulting from exposure in the developing lung. As she explained, lung development takes up to three years in humans and ten days in rats, creating a window of enhanced susceptibility to the adverse effects of PM exposure.

“Asthma and related respiratory diseases affect 100 to 150 million people worldwide and 20 million in the United States alone,” Cormier explained. These diseases are responsible for an estimated health care cost of \$16.1 billion annually, “more than the health care costs associated with HIV/AIDS and tuberculosis combined.” She added that the dramatic increase in these diseases in recent years — “50 percent per decade” — argues against genetic drift as a primary cause and points to the involvement of environmental factors.

The experiments by Cormier’s group exposed 7-day-old Norway Brown rats 20 minutes per day for one week to DCB230 — a combustion-generated engineered PM 0.1 containing free radicals. Cormier said using the DCB230 surrogate eliminated the size and sample variability and chemical complexity of PM collected in the atmosphere. With the engineered pollutant particle system, she was able to associate a specific PM component with downstream effects on protein expression and control for aggregation.

On day 15, the research team isolated and analyzed rodent lungs with a proteomics strategy and identified genes with expression differences of at least 0.3 fold. The team found variation in 16 proteins between DCB230 and vehicle — a copper oxide/silica substrate that causes a very limited inflammatory response.

Among the proteins of interest affected by DCB230 exposure were Hsp 60, a heat-shock protein implicated in mitochondrial protein folding; annexin VII, a protein expressed in response to reactive oxygen species; and cofilin-1, a protein associated with COPD and dexamethsone insensitive asthma. Changes in the expression of other markers of oxidative stress and inflammation were also observed.

Cormier said the results are consistent with her hypothesis that persistent semiquinone-type radicals generate intracellular reactive oxygen species triggering oxidative stress in the neonatal lung. This oxidative stress in turn causes the lung to undergo structural changes and permanent alteration of adaptive immune response, leading to hyper-responsiveness. These changes contribute to the airflow limitation and long-term lung dysfunction found in patients with asthma and COPD.

“The observed proteome changes following exposure to DCB230 indicate a link to the protein-misfolding diseases and may therefore present common targets for therapeutic intervention,” she concluded. The findings may also have implications in the determination of air quality standards for PM 0.1, which is not currently regulated.

Coauthors of the study include LSU Postdoctoral Fellow Shrilatha Balakrishna, Ph.D., research specialist Terry Ahlert, Ph.D. students Dahui You and Baher Fahmy, Danielle Major, LSU chemist Slawo Lomnicki and environmental scientist Barry Dellinger, Ph.D.

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Cormier is helping to answer the critical questions in air pollution research — how PM triggers adverse health effects in the human body and why some groups are more susceptible than others. (Photo courtesy of Steve McCaw)

Findings Show Protection Against Oxidative Stress

By *Negin Martin*

High levels of reactive oxygen species (ROS) are implicated in cardiovascular and neurodegenerative disease and are proposed to accelerate aging and promote cancer, according to new [NIEHS-funded](#) research published in *PLoS Genetics*. Led by Trey Ideker, Ph.D., the study identified the components of a remarkable pathway that triggers adaptation and protects cells against acute oxidative stress. The study's findings point to the possibility that manipulating the function of the identified genes has the potential to lower incidence of disease and to prolong life.

[Ideker](#) is chief of the Division of Genetics in the Departments of Medicine and Bioengineering at the University of California, San Diego (UCSD) and a member of the Moores UCSD Cancer Center. His innovative use of genomic and bioinformatic approaches has yielded deep insights into molecular pathways and disease.

In the [study](#), Ideker examined the mechanism of adaptation to oxidative stress using yeast as a model organism. His findings demonstrate that pretreatment of yeast with low levels of hydrogen peroxide, as a source of oxidative stress, protects yeast against acute doses of hydrogen peroxide. Low levels of oxidants trigger an adaptive response that is not active during high-dose treatments.

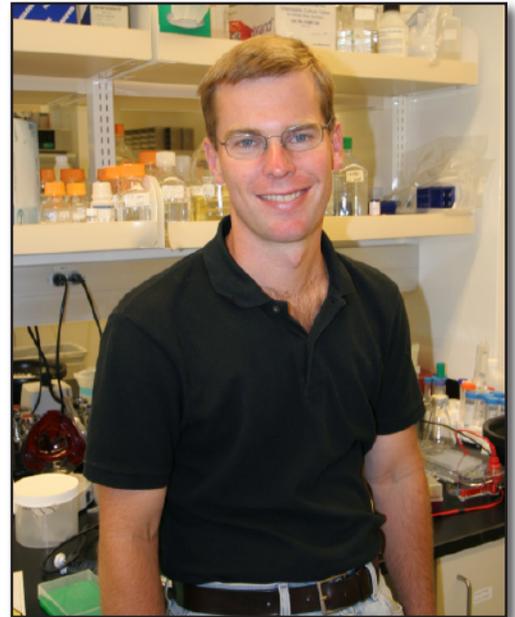
“Our study runs counter to the conventional wisdom that antioxidants are good for you,” Ideker said of his findings. “It appears that at least a small amount of oxidant can have beneficial effects.”

Genetic screening of 4,831 single-gene deletion strains of yeast revealed that mild/adaptive exposures and acute exposures activate different pathways inside the cell. The adaptive pathway requires the presence of transcriptional regulators such as Yap1, Skn7, Rox1, and especially Mga2 — a previously identified response gene expressed in hypoxia.

Mga2 targets the metabolism of a cholesterol-like compound, ergosterol, that gets incorporated into the plasma membrane and makes it more rigid. Ideker hypothesizes that pretreatment of yeast with hydrogen peroxide potentiates Mga2 and increases ergosterol levels. Increase in membrane rigidity, due to ergosterol incorporation, inhibits the diffusion of H₂O₂ across the membrane and entry into the cell. Indeed, direct measurement of ergosterol levels shows lower concentrations in *mga2* and *rox1* deleted strains.

Mga2 also regulates the components of fatty acid pathway that may contribute to changes in the permeability and stability of cellular membranes. Exposure to low doses of ROS – generated by H₂O₂ in this study – can help cells adapt to the environment by changing the membrane structure and making it more resistant to higher doses of ROS. Ideker plans to test this hypothesis in higher organisms.

Oxidative stress and generation of ROS are important factors in aging. Because of their role, a general assumption has been that by lowering the levels of ROS, one can extend lifespan.



Ideker, shown in his lab at UCSD, also spoke at NIEHS in 2007 as part of a [symposium on systems biology](#) organized and hosted by Center for Risk and Integrated Sciences Program Administrator David Balshaw, Ph.D. (Photo courtesy of UCSD)

ROS or oxidants are byproducts of normal metabolic processes. The highly reactive nature of oxidants is damaging to cells, and they are therefore promptly converted to less reactive species by specialized enzymes — superoxide dismutases, catalases, and various peroxidases — inside the cell. Organs with high metabolic rate such as brain are especially vulnerable to damage by oxidants. Antioxidants, such as vitamin C, E and glutathione, can help cells lower the levels of oxidants.

Citation: Kelley R, Ideker T. 2009. Genome-wide fitness and expression profiling implicate Mga2 in adaptation to hydrogen peroxide. PLoS Genet 5(5):e1000488. doi:10.1371/journal.pgen.1000488. Epub May 29.

(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.)

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Expert Panel Reviews Glass Wool Fibers

By Robin Mackar

An expert panel convened in Chapel Hill, N.C. on June 9–10 by the National Toxicology Program (NTP) to review the scientific literature and consider a recommendation by the North American Insulation Manufacturers Association to change the listing status for glass wool fibers in the upcoming *12th Report on Carcinogens (RoC)*. The expert panel decided to make separate recommendations for different categories of glass wool fibers.

The panel recommended by a unanimous vote that most glass wool fibers should not be classified either as “known to be a human carcinogen” or as “reasonably anticipated to be a human carcinogen,” and should be removed from the RoC listing. Glass wool of respirable size is currently listed in the *11th RoC* as “reasonably anticipated to be a human carcinogen.”

However, the panel made a distinction for special glass wool fibers of concern, which they defined as longer, thinner, and less soluble fibers. The expert panel recommended that glass fibers with these characteristics — 15 millimeter or greater in length with a dissolution rate equal to or less than 100 nanograms per square centimeter per hour — are listed as “reasonably anticipated to be a human carcinogen” in the 12th RoC. The vote was seven to zero with one abstention, with panel members citing sufficient evidence of carcinogenicity in well-conducted animal inhalation studies as the basis for the recommendation.

After receiving oral public comments from a number of groups, the glass wool fibers expert panel carried out an in-depth review of the draft background document and voted unanimously to accept the background document with the panel’s suggested changes. They then discussed the scientific information for glass wool fibers, applied the RoC listing criteria to the body of evidence, and made a recommendation for listing status in the RoC.



Expert Panel members come and go, but RoC Group Director Ruth Lunn, Dr.P.H., sits center stage during long days full of scientific discussion as each compound is considered for listing. (Photo courtesy of Steve McCaw)

Glass wool refers to fine glass fibers forming a mass resembling wool and is most commonly used for insulation and filtration. There are two categories of glass wool based upon commercial application — insulation glass wool, which is now among the most extensively used insulating material worldwide, and special-purpose fibers, which are used in special applications and make up a much smaller fraction of the market. There are differences in the chemical compositions and physical characteristics of glass fibers, which may influence the toxicology and potential carcinogenicity of different fibers.

Fibers have also been examined based upon other characteristics including persistence, retention and clearance rates, and durability. The European Union and Germany have established criteria for labeling and classifying synthetic vitreous fibers based on their potential human health hazard.

Next, the NTP will solicit public comment on the expert panel's listing recommendation and scientific justification through the *Federal Register* and finalize the background document, taking into consideration the panel's recommended edits and public comments. Afterwards, the agency will convene two independent review groups who will also apply the RoC listing criteria and make a recommendation for listing status in the RoC.

Information about this meeting and the review of wool glass fibers or any other RoC nominated chemical is available [online](#).

(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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Facing a bank of microphones, Expert Panel Chair Karl Kelsey, M.D., center, studies documents related to the report on glass wool fibers. Kelsey is a professor of Community Health and Pathobiology and Laboratory Medicine at Brown University. (Photo courtesy of Steve McCaw)



Expert Panel member Morton Lippmann, Ph.D., seeks clarification during the question-and-answer segment of a presentation. Lippmann is a professor of Environmental Medicine at the New York University Langone Medical Center. (Photo courtesy of Steve McCaw)



NTP support staff at the meeting included, left to right, former RoC Group Director Bill Jameson, Ph.D., who is now a consultant, Health Scientist Diane Spencer and Deputy Program Director for Policy Mary Wolfe, Ph.D. (Photo courtesy of Steve McCaw)

NIEHS-Funded Imaging Tool Logs 100,000th Job

By Eddy Ball

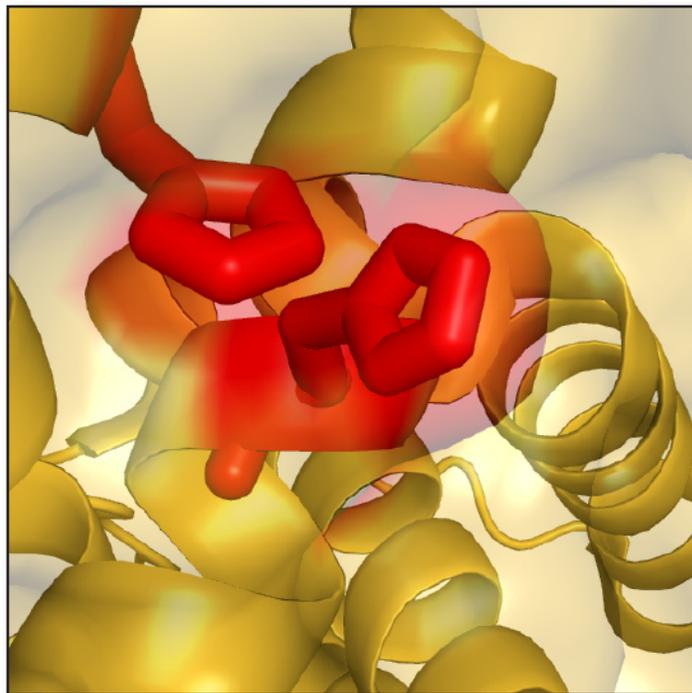
The NIEHS-funded University of Cincinnati (UC) Center for Environmental Genetics (CEG) announced that its Bioinformatics Core recorded its 100,000th job submission on June 11 for its popular POLYVIEW-3D imaging tool. POLYVIEW-3D is a Web-based macromolecular-structure visualization and analysis tool developed by UC professors as part of a series of expanded, user-friendly Web-based software applications and servers that scientists and students can use, free of charge, to extract and extrapolate structural and functional genomic data for various research projects.

POLYVIEW-3D developers Alexey Porollo, Ph.D., the primary architect of the product, Jarek Meller, Ph.D., and Mario Medvedovic, Ph.D., are professors in the Division of Epidemiology and Biostatistics in the UC Department of Environmental Health. In an August 2007 article published in the open access journal *BMC Bioinformatics*, Porollo and Meller announced the availability and terms of use for POLYVIEW-3D.

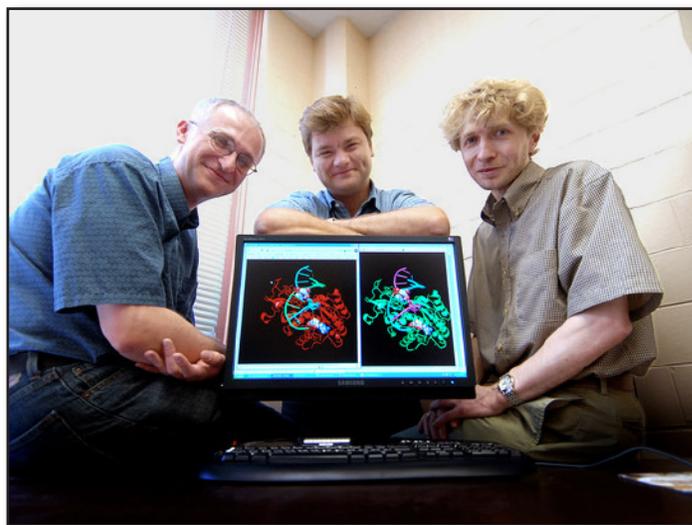
“We’re making them [existing bioinformatics tools] better and developing new methods for analyzing the data,” Porollo explained. “A growing base of users, and cross-linking by major proteomic resources such as the Protein Data Bank and various prediction meta-servers, are evidences of the competitiveness of our tools.”

One of the nation’s leading structural biologists, NIEHS Principal Investigator Samuel Wilson, M.D., is one of many scientists who agree with Porollo. “POLYVIEW-3D is an important tool in making the incredible excitement of structural biology more accessible for scientists, students and the public at large,” he said.

By integrating the Web technology with state-of-the-art software for macromolecular visualization, POLYVIEW-3D enables versatile structural and functional annotations of proteins and their complexes, coupled with publication-quality structure rendering. In addition to static pictures, high quality animated images for electronic resources such as PowerPoint or Websites can be easily generated.



“Structure of the Native and Inactive LicT PRD from *B. Subtilis*”
Two histidine residues shown in red undergo phosphorylation that induces dramatic conformational change and regulates the dimerization of LicT regulatory domain — LicT-PRD, PDB id 1tlv. (Image courtesy of Jarek Meller)



From left to right, POLYVIEW-3D developers Medvedovic, Porollo, who is a CEG Next-Generation Biomedical Investigator, and Meller pose with a computer showing images generated by their tool. (Photo courtesy of UC)

In particular, POLYVIEW-3D server features the PyMol program for image rendering, providing detailed and high quality slide and animated presentations of macromolecular structures, with an easy to use Web-based interface.

POLYVIEW-3D was voted one of the top five protein structure visualization/annotation resources by MolviZ.org, where it is described as “easy enough for student reports or homework assignments!” There is no need for users to know any command language to use the free service — just a user-friendly form to fill out online. According to Porollo, the tool has been used by researchers in over 80 countries this year alone, and several universities include the server as part of the curriculum in practical courses on macromolecular visualization.

Citation: [Porollo A, Meller J. 2007. Versatile annotation and publication quality visualization of protein complexes using POLYVIEW-3DBMC *Bioinformatics* 8:316. doi:10.1186/1471-2105-8-316.](#)

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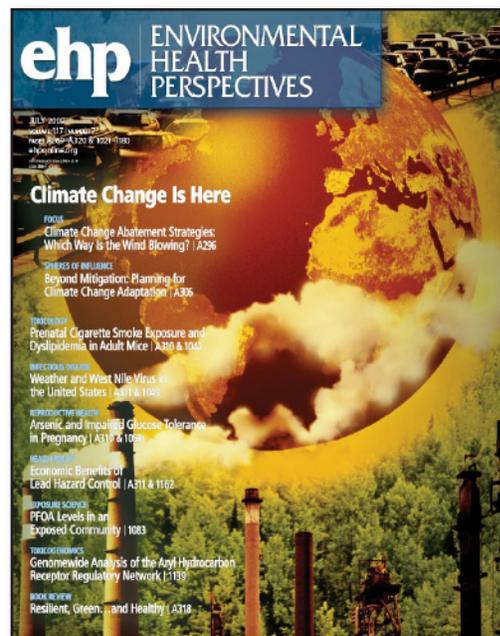
This Month in EHP

By Eddy Ball

The July 1 issue of *Environmental Health Perspectives (EHP)* develops the theme “Climate Change Is Here,” with a Focus article on climate change abatement strategies and a Spheres of Influence feature exploring the challenge of adapting to climate change already underway.

Highlights from the issue include the following studies:

- Toxicology — Examining prenatal exposure to cigarette smoke and risk of cardiovascular disease later in life
- Infectious Disease — Modeling the impact of warmer temperatures, elevated humidity and heavy precipitation on the spread of West Nile Virus in the U.S.
- Reproductive Health — Evaluating the association of arsenic exposure and increased risk for development of gestational diabetes
- Health Policy — Reporting a cost-benefit analysis of measures to reduce lead paint exposures in terms of reduced cost for healthcare, crime control, special education and Attention Deficit Hyperactivity Disorder (ADHD) treatment
- Exposure Science — Measuring serum perfluorooctanoic acid levels in residents near a Teflon manufacturing plant in the Ohio valley
- Toxicogenomics — Using genomewide analysis to characterize the aryl hydrocarbon receptor regulatory network in the presence and absence of xenobiotic stimulation



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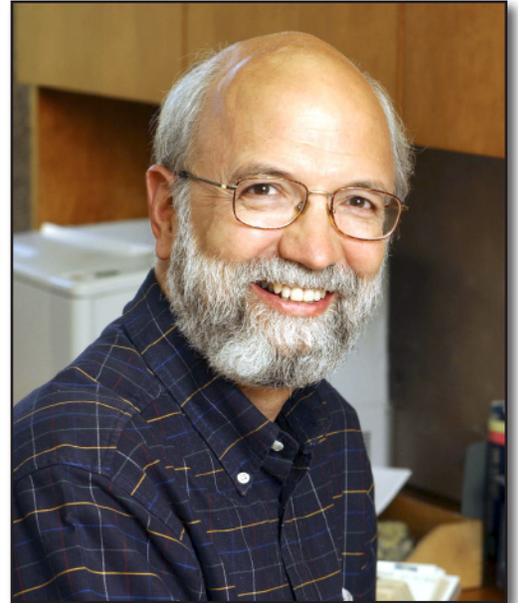
Wilcox to Speak at Science Café July 14

By Eddy Ball

Science goes informal each month at Durham's Broad Street Café, which will host a talk by NIEHS Senior Investigator and epidemiologist [Allen Wilcox, M.D., Ph.D.](#), at 7:00 p.m. on July 14. Wilcox will be discussing the key steps of human conception and early pregnancy, including the new options for infertile couples made possible through modern technology.

Wilcox has devoted his training as a pediatrician, public health specialist and epidemiologist to a 30-year career unraveling the mysteries of reproductive and infant health and identifying the potentially preventable environmental exposures that affect outcomes. He has published over 160 articles in peer-reviewed journals and contributed chapters to 11 books.

A new book by Wilcox, *Fertility and Pregnancy: An Epidemiologic Perspective*, is now in the process of publication by Oxford University Press. He has received a long list of honors, including an honorary doctor of philosophy [degree](#) awarded in 2008 by the University of Bergen in Norway in recognition of his "contributions toward making epidemiology one of the central disciplines of modern medicine."



Wilcox joined NIEHS as a research medical officer in 1979 and has held adjunct positions at his alma mater, the University of North Carolina at Chapel Hill, and at the University of Bergen. (Photo courtesy of Steve McCaw)

Wilcox's talk is part of the monthly [Periodic Tables series](#) sponsored by the Museum of Life and Science in Durham. The museum describes the series as monthly gatherings "where curious adults can meet in a casual setting to discuss the latest science in plain English... and there is no such thing as a stupid question." [Broad Street Café](#) is located just [north of downtown Durham](#) between the Durham Expressway and Interstate 85.

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Extramural Update

Endocrine Disruptor Research: It's Not Just Toxicology

The scientific statement "Endocrine Disrupting Chemicals: An Endocrine Society Scientific Statement," which was announced at a news conference June 10 by Robert M. Carey, M.D., president of The Endocrine Society, and published in the journal *Endocrine Reviews*, marks an important step forward for research on endocrine disruption. The article reviews the data on endocrine disrupting chemicals (EDCs) and human health and identifies research needs and data gaps. This [statement](#) was developed because of the society's belief that there is concern for human health from exposures to EDCs (see [related story](#)).

EDCs are exogenous substances that act like hormones in the endocrine system, disrupting the physiological function of endogenous hormones. EDCs encompass a variety of chemical classes such as pesticides and plant constituents, as well as compounds used in plastics and many consumer products.

EDC research evolved from the integration of researchers from many scientific disciplines — such as human reproductive biology, wildlife/comparative endocrinology and ecotoxicology, and rodent toxicology — brought together at meetings sponsored by either private funding or by the NIEHS. These forums included the Wingspread meetings organized by the World Wildlife Fund and Estrogens in the Environment I, II and III sponsored by NIEHS.

After the book *Our Stolen Future* was published in 1995 and the National Academy of Sciences issued its 1999 report, *Hormonally Active Agents in the Environment*, a groundswell of activity began with major symposia held by such organizations as The Society of Toxicology (SOT), the Society of Environmental Toxicology and Chemistry, and the Society for Integrative and Comparative Biology.

The NIEHS developed three initiatives and held numerous workshops and meetings over the next decade, to focus attention on this emerging field. Today the NIEHS continues to be the major source of funding of EDC research.

Recently, societies focused on endocrinology and reproductive biology have highlighted EDC research at their national meetings:

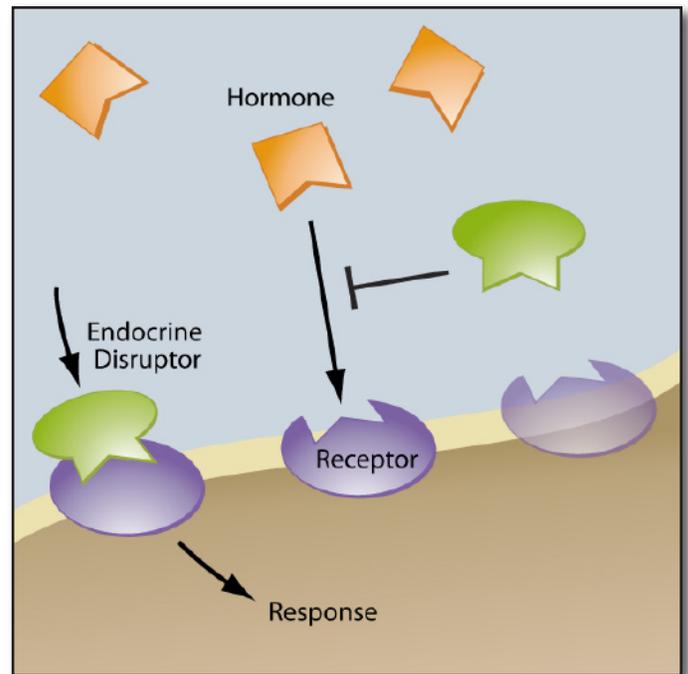
- The American Thyroid Association (ATA) held a session on the role of environmental chemicals in altered thyroid function at its Research Summit earlier this year.
- The American Society for Reproductive Medicine (ASRM) and the Society for the Study of Reproduction organized special interest groups to develop a focus on environmental exposures at their national meetings.
- At the ASRM national meeting in 2008, a review article, “Female reproductive disorders: The role of endocrine disrupting compounds and developmental timing,” and the “Proceedings of the Summit on Environmental Challenges to Reproductive Health and Fertility: Executive Summary” were included as special contributions to the ASRM journal, *Fertility and Sterility*. These articles explored the role of EDCs in female reproductive diseases and identified research needs and data gaps.

In 2005, the Endocrine Society hosted the first EDC forum and published the proceedings in *Endocrinology*. Since that time the Endocrine Society has hosted keynote speakers, along with oral and poster sessions on EDCs. In 2007, the European Obesity Society cosponsored a day-long workshop on “Endocrine Disruption from the Environment and the Aetiology of Obesity and Diabetes.” This year the Endocrine Society featured “The 2nd Endocrine Society Forum on Endocrine Disruptors: Best Science for Risk Management and Policy.” This forum was cosponsored by the ATA, the Society for the Study of Reproduction and the SOT.

EDC research is not just toxicology anymore. NIEHS is pleased to see the increased concern by clinical, reproductive and endocrine societies about the possible adverse effects of EDCs on human disease. This concern creates a win-win situation that brings scientists with new backgrounds and new approaches to the field.

Contact: [Jerrold Heindel, Ph.D.](#)

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Extramural Papers of the Month

By Jerry Phelps



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

- [Dioxins in Food Chain May Cause Poor Milk Production](#)
- [Genome-Wide Association Study Identifies Asthma Gene](#)
- [Glutathione S-Transferase Polymorphism Increases Risk of Second Primary Malignancy](#)
- [PCBs May Alter *in utero* Neonatal Brain Development](#)

Dioxins in Food Chain May Cause Poor Milk Production

An NIEHS-funded research team at the University of Rochester Medical Center reports that exposure to dioxins during pregnancy harms rapidly growing and dividing epithelial cells in breast tissue, which may explain why some women have trouble breastfeeding or have poor milk production.

The studies were performed using laboratory mice and show that early administration of dioxin caused mammary cells to stop proliferating as early as six days into the pregnancy and lasted through mid-pregnancy. The researchers also determined that dioxin inhibited the induction of genes involved in milk production and decreased the number of ductal branches and mature lobules in mammary tissue. The studies show that induction of the Ah receptor was crucial in producing the effect and that timing of the exposure was important.

Estimates suggest that three to six million mothers worldwide are unable to breastfeed or are unable to produce enough milk to nourish their babies. Breastfeeding has been shown over and over again to have positive benefits for mother-child bonding and for the overall health of the child. Further research is necessary to find a link between dioxin exposure and problems with breastfeeding in women.

Citation: [Lew BJ](#), [Collins LL](#), [O'Reilly MA](#), [Lawrence BP](#). 2009. Activation of the aryl hydrocarbon receptor (AhR) during different critical windows in pregnancy alters mammary epithelial cell proliferation and differentiation. *Toxicol Sci Jun 5*. Epub ahead of print.

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Genome-Wide Association Study Identifies Asthma Gene

A multicenter study identified two single nucleotide polymorphisms of a gene known as phosphodiesterase 4D or *PDE4D* as an asthma susceptibility gene in a large genome-wide association study. *PDE4D* is a regulator of airway smooth muscle contractility and medications targeted towards inhibition of the enzyme have been developed to treat asthma, which affects approximately one out of 20 people worldwide.

The economic impact of this disease from lost work productivity as a result of the disease or from caring for a child with asthma is staggering. Previous studies have identified over 40 genes associated with asthma.

A genome-wide association study is an approach that involves scanning markers across the complete genome of many people to find genetic variations they have in common associated with a particular disease. Once the genetic associations are identified, the information is used to develop better strategies to detect, treat and prevent disease. These studies have proven particularly useful in finding genetic variations that contribute to complex diseases such as asthma, cancer, diabetes, heart disease and mental illnesses.

Two single nucleotide polymorphisms proved to be highly statistically significant with respect to asthma in a combined population of over 18,000 white and Hispanic subjects. Further study of the polymorphisms of *PDE4D* will lead to an improved understanding of the gene's role in asthma and the efficacy of *PDE4D* inhibitors in treating asthma.

Citation: Himes BE, Hunninghake GM, Baurley JW, Rafaels NM, Sleiman P, Strachan DP, Wilk JB, Willis-Owen SA, Klanderma B, Lasky-Su J, Lazarus R, Murphy AJ, Soto-Quiros ME, Avila L, Beaty T, Mathias RA, Ruczinski I, Barnes KC, Celedón JC, Cookson WO, Gauderman WJ, Gilliland FD, Hakonarson H, Lange C, Moffatt MF, O'Connor GT, Raby BA, Silverman EK, Weiss ST. 2009. Genome-wide association analysis identifies *PDE4D* as an asthma-susceptibility gene. *Am J Hum Genet* 84(5):581-593.

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Glutathione S-Transferase Polymorphism Increases Risk of Second Primary Malignancy

A large prospective cohort study suggests that people with certain polymorphisms of the glutathione S-transferase (GST) genes are more likely to develop a second primary malignancy after first developing squamous cell carcinoma of the head and neck. The study reports a 1.7-fold increase for people with the *GSTP1* Ile(105)Val polymorphism and an even greater risk for multiple *GST* risk genotypes.

Most squamous cell carcinomas of the head and neck area are attributable to tobacco and alcohol. However, most smokers and drinkers never develop squamous cell carcinoma, suggesting that genetic susceptibility plays a significant role in the development of the cancer. Traditional cancer therapies cure many squamous cell carcinomas, but a significant proportion of patients go on to develop a second primary malignancy.

GSTs are known to detoxify many carcinogens in tobacco smoke. The research team hypothesized that variations in the genes coding for GSTs might alter a person's risk for developing a second malignancy. Identifying markers of risk for later malignancies among cancer survivors could greatly enhance secondary cancer prevention efforts. By screening patients for these genetic variations, physicians could identify those patients more likely to develop additional cancers and target them for more stringent intervention regimens and closer follow-up, to prevent additional cancers or identify them at earlier stages.

Citation: Zafereo ME, Sturgis EM, Aleem S, Chaung K, Wei Q, Li G. 2009. Glutathione S-transferase polymorphisms and risk of second primary malignancy after index squamous cell carcinoma of the head and neck. *Cancer Prev Res (Phila Pa)* 2(5):432-439.

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PCBs May Alter *in utero* Neonatal Brain Development

In three new studies, NIEHS grantees at the University of California, Davis provide evidence of how low-level exposure to polychlorinated biphenyls (PCBs) alters the normal development of brain cells. These findings could help to explain the relationship between PCB exposure and neurodevelopmental and behavioral disorders in children.

Although PCBs were banned 30 years ago, researchers have never understood the mechanism by which PCBs produce neurological problems in children. The researchers exposed laboratory rats to low levels of two structurally different PCBs and examined the hippocampus, a region of the brain involved in memory and learning. They found that PCB exposure locks ryanodine receptors, a class of intracellular calcium channels that control the electrical excitability of neurons, into the “on position” thus altering their excitability. Additional *in vitro* studies confirmed the results.

The team plans to conduct additional studies in mice that carry some of the same genetic variations of the ryanodine receptors that humans exhibit. Those studies will be important to determine whether there are people who are genetically susceptible to PCB toxicity.

Citation: Kim KH, Inan SY, Berman RF, Pessah IN. 2009. Excitatory and inhibitory synaptic transmission is differentially influenced by two ortho-substituted polychlorinated biphenyls in the hippocampal slice preparation. *Toxicol Appl Pharmacol* 237(2):168-77.

(Jerry Phelps is a program analyst in the NIEHS Division of Extramural Research and Training. Each month, he contributes summaries of extramural papers to the *Environmental Factor*.)

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Intramural Papers of the Month

By Robin Arnette

- [Anti-Hu is a Possible Marker for Small Cell Lung Cancer](#)
- [Environmental and Genetic Factors Are Basis of Disease](#)
- [Hyaluronan Contributes to Murine Airway Hyperresponsiveness](#)
- [Development of Polycystic Kidney Disease and Type I Diabetes in Glis3-Deficient Mice](#)

Anti-Hu is a Possible Marker for Small Cell Lung Cancer

Antibodies against Hu proteins (anti-Hu) are a potential marker for small cell lung cancer (SCLC) according to a team of scientists from NIEHS, the University of Southern California and the University of California Los Angeles. Since SCLC is one of the fastest and deadliest cancers, finding this marker could improve survival in SCLC patients.

Hu proteins, a family of RNA-binding proteins, are homologous to the embryonic lethal abnormal visual (ELAV) protein in *Drosophila* and are involved in neuron-specific RNA processing and neural development. Previous studies from other labs had determined that SCLC tumors express Hu proteins and that anti-Hu reactivity occurred in 17– 25.5 percent of SCLC patients.

To find out whether anti-Hu antibodies were associated with an increased risk of developing SCLC, the investigators analyzed levels of anti-Hu antibodies in 41 SCLC patients and 79 matched population controls. The team used recombinant HuD protein, one of the four Hu proteins, in a Western blot analysis and determined that 15 percent of SCLC patients had detectable anti-Hu activity.

The research is the first report of a correlation between anti-Hu reactivity and SCLC in a population-based study, but the authors point out that large-scale studies are needed to determine if anti-Hu profiles can be used as a SCLC detection marker.

Citation: [Tsou JA, Kazarian M, Patel A, Galler JS, Laird-Offringa IA, Carpenter CL, London SJ. 2009. Low level anti-Hu reactivity: A risk marker for small cell lung cancer? Cancer Detect Prev 32\(4\):292-299.](#)

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Environmental and Genetic Factors Are Basis of Disease

Using several databases and analysis algorithms, scientists from NIEHS, the National Institute on Aging and the Mount Desert Island Biological Laboratory have identified significant molecular pathways that link human disease with environmental factors and genetics. The authors argue that knowledge-based, systems-driven evaluations like the one presented in the publication, will improve public health by offering promising areas of research.

The research team used Structurally Enhanced Pathway Enrichment Analysis (SEPEA) to analyze gene-phenotype relationships found in the Genetic Association Database (GAD). The investigators also studied how environmental and genetic susceptibility factors contribute to a specific phenotype, by identifying pathways of environmental factor-gene protein relationships in the Comparative Toxicogenomics Database. The result was an interactome describing the relationships between human disease and environmental exposure mediated through metabolic and signal-transduction pathways.

The evaluation resulted in several clusters, such as immune related pathways (e.g. Toll-like receptor signaling) resulting in autoimmune diseases as well as cardiovascular, kidney and Alzheimer's disease. The work identified seemingly unrelated clusters (e.g. neuropsychiatric disorders, obesity and lung disease) that create hypotheses for future research.

Citation: [Gohlke JM, Thomas R, Zhang Y, Rosenstein MC, Davis AP, Murphy C, Becker KG, Mattingly CJ, Portier CJ. 2009. Genetic and environmental pathways to complex diseases. BMC Syst Biol 3:46; doi: 10.1186/1752-0509-3-46 \[online 5 May 2009\].](#)

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Hyaluronan Contributes to Murine Airway Hyperresponsiveness

Researchers from NIEHS, Duke University, Aichi Medical University in Japan, the University of Texas Southwestern Medical Center and the National Jewish Medical and Research Center have discovered that hyaluronan, an abundant extracellular matrix component, mediates ozone-induced airway hyperreactivity (AHR). The work sheds more light on the pathogenesis of environmental airway disease and is the first study to show that short fragments of hyaluronan contribute to AHR following ozone exposure.

The collaborative team found that mice exposed to ozone had high levels of hyaluronan in lung lavage fluid and exhibited AHR. Mice that were deficient in CD44, a hyaluronan receptor, and inter- α -trypsin inhibitor (IaI), a molecule that facilitates hyaluronan binding, also had elevated levels of hyaluronan in the lavage fluid, but were protected from ozone-induced AHR.

The size of the hyaluronan fragment instilled into the lung was also found to determine whether AHR occurred after ozone exposure — low molecular weight hyaluronan induced AHR after ozone, while high molecular weight hyaluronan protected against the disorder. These data have identified hyaluronan as a potential target for the treatment of AHR.

Citation: [Garantziotis S, Li Z, Potts EN, Kimata K, Zhuo L, Morgan DL, Savani RC, Noble PW, Foster WM, Schwartz DA, Hollingsworth JW](#). 2009. Hyaluronan mediates ozone-induced airway hyperresponsiveness in mice. *J Biol Chem* 284(17): 11309-11317.

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Development of Polycystic Kidney Disease and Type I Diabetes in Glis3-Deficient Mice

Glis3 is a member of a subfamily of Krüppel-like zinc finger transcription regulators previously identified by the Jetten lab at NIEHS. The researchers generated mutant mice (Glis3^{z/zf}) that were deficient in Glis3, and the mice exhibited characteristics similar to those observed in patients with the disorder “neonatal diabetes and congenital hypothyroidism” (NDH). As in NDH patients, these mutant mice had a short life span and developed Type I diabetes and polycystic kidney disease (PKD).

Studies from other labs found a link between proteins involved in cystic renal diseases and signaling pathways associated with the primary cilium, a sensory organelle that is part of most cells. The concept was substantiated in this study when Glis3 was found to be associated with the primary cilium in renal tubules, suggesting that Glis3 is part of a primary cilium signaling pathway.

In addition, the team found the connection between Glis3 and the transcriptional modulator Wwtr1. Both Glis3^{z/zf} and Wwtr1 null mice developed glomerulocysts. Co-immunoprecipitation and mammalian two-hybrid analyses confirmed that Glis3 and Wwtr1 were part of the same complex. Pull-down and point mutation analysis demonstrated that Glis3 directly interacts with Wwtr1. The investigators subsequently demonstrated that Wwtr1 functioned as a coactivator of Glis3-mediated transcription.

Citation: [Kang HS, Beak JY, Kim YS, Herbert R, Jetten AM](#). 2009. Glis3 is associated with primary cilia and Wwtr1/TAZ and implicated in polycystic kidney disease. *Mol Cell Biol* 29(10):2556-2569.

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Inside the Institute

Program Celebrates Asian and Pacific Islander Heritage

By Eddy Ball

NIEHS commemorated Asian/Pacific Islander Heritage Month on May 27 with a talk on Oriental medicine in Rodbell Auditorium, followed by ethnic food sampling and a hula dance performance and instruction in the NIEHS cafeteria. The theme of the 2009 celebration sponsored by the [NIEHS Diversity Council](#) was “Leadership to Meet the Challenges of a Changing World.”

Hosted by NIEHS [Special Techniques Group](#) Biologist and Asian/Pacific Islander Heritage Month committee member Eli Ney, the talk by licensed acupuncturist and performance technologist Brian Kramer explored “The Science of Acupuncture: A Comparative Analysis of Acupuncture in Biomedicine and Traditional Approaches.” Kramer’s practice in Raleigh combines acupuncture, herbal medicine, fitness training, nutrition, and medical massage and rehabilitation techniques.

Kramer tied his talk into the challenges of a changing world by pointing to the increasing acceptance of Oriental medicine as a part of an integrated, holistic approach to promoting healing and wellness for the individual. “Oriental medicine, including traditional Chinese medicine,” he explained, “enhances and accelerates the body’s own healing wisdom by addressing the body as a whole and the balance of physical, mental and emotional health.”

Kramer said more and more patients are recognizing the shortcomings of the symptom-centered allopathic medicine approach and looking to alternative sources, as they come to understand that “wellness is more than simply the absence of disease.” He referred to the growing body of information about acupuncture and Oriental medicine as well as clinical studies supported by the [NIH National Center for Complementary and Alternative Medicine](#).

Following Kramer’s talk, the celebration moved to the NIEHS cafeteria, where the promise of food and entertainment drew even more people. As NIEHS employees and contractors sampled ethnic specialties and desserts, they talked and mingled while Enloe High School student Serina Ann Durrett queued the music for her hula performance. Durrett’s performance was hosted by Asian/Pacific Islander Heritage Month committee member and NIEHS staffer Myra Westmoreland.



Kramer, above, criticized the shortcomings of conventional studies of Oriental medicine. “All the data is fine,” he said, “but I’m a clinician concerned with the individually specific effects of a therapy.” (Photo courtesy of Steve McCaw)



The lecture drew NIEHS employees with ties to, or interest in, Asian/Pacific Islander cultural heritage, such as NIEHS Postdoctoral Fellow Reuben Thomas, Ph.D., right, and JinJie Jiang, Ph.D. (Photo courtesy of Steve McCaw)

Durrett performed two numbers before taking a break and changing her costume for the instructional part of her visit to NIEHS. She was joined on stage by several enthusiastic attendees eager to enjoy a break from routine and pick up new moves for their dancing repertoire.



Following her first performance and a change of clothes, Durrett took the microphone and invited volunteers to take the stage along with her. (Photo courtesy of Steve McCaw)



NIEHS Toxicologist James Huff, Ph.D., above, responded to Kramer's statement that "Oriental medicine is very good with viral infection" with a question on treating the H1N1 virus with acupuncture and herbs. (Photo courtesy of Steve McCaw)



Ney took advantage of Durrett's instruction and donned a Hawaiian lei as she practiced hula moves for the audience. (Photo courtesy of Steve McCaw)



Esther Hou, an NIEHS biologist in the DNA Repair and Nucleic Acid Enzymology Group, relaxed as she watched the demonstration. (Photo courtesy of Steve McCaw)



NIEHS Employee Services Manager Dona McNeill seemed ready to embrace the new experience of hula dancing. (Photo courtesy of Steve McCaw)



NIEHS Employee Services Intern Jennifer Evans seemed to enjoy her first taste of Diversity Council celebrations, as she watched her supervisor get into the swing and sway of things. Evans is a senior at the University of North Carolina at Greensboro majoring in Human Development and Family Studies. (Photo courtesy of Steve McCaw)

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Another Scorching Friends and Family Day

By Eddy Ball

No one actually plans it that way, but NIEHS Friends and Family Day, which moved outdoors in 2007, always seems to coincide with some of the hottest days of summer. The 2009 celebration was no exception, as NIEHS staff and contractors, families and children, and friends gathered under a sweltering sun June 19 on the patio outside the Rall building for fellowship, music, snacks, games and fishing. There were lunch specials at the NIEHS cafeteria inside, and those who wanted to escape the oppressive heat could enjoy Wii dancing and bingo in air-conditioned comfort in Rodbell Auditorium.

NIEHS and National Toxicology Program (NTP) Director Linda Birnbaum, Ph.D., kicked off the event. “I’m a little sorry for the weather,” she said and warned attendees to avoid getting overheated as they enjoyed the event. Speaking optimistically, she warned the other teams in the annual softball game to watch out for her Office of Director (OD) and NTP team, which she promised would pummel posteriors when the competition got underway later in the afternoon.

As the thermometer topped 90 degrees, the action shifted to the NIEHS ball field where the Institute’s softball warriors battled for the honor of besting their colleagues from other divisions. Elimination games left members of the Division of Extramural Research and Training (DERT) Devils and the Division of Intramural Research (DIR) Discoverers sitting on the sidelines for the final competition.



NIEHS staffer Jeannie “J.J.” Bell-Nichols watched over the prizes for the cake walk competition, as a fan in the background struggled to cool the karaoke stage and sound control area. (Photo courtesy of Steve McCaw)

Not even a new name and Birnbaum's enthusiastic boosterism could tip the scales for OD/NTP in the playoff game. In a 23 to 2 rout, the Office of Management's (OM) Blazin' Bullets hitting machine trounced the OD/NTP Riptides and came away with the winner's cup for the second time in the three-year series. The outcome showed that enough new talent and fresh faces can revitalize a losing team.

Fortunately, as organizer Steve McCaw said afterwards, the annual battle of the bats "is indeed a Family Day event with just enough competition to make things 'edgy'" — so if there were any hurt feelings and injured pride, they shouldn't linger for long.



"It's really fun to see people and their families here," Birnbaum said as she told the audience that her husband and mother were also visiting NIEHS that day. Birnbaum turned out to be a gracious host, but a victim of wishful thinking and fond illusion when it came to softball. (Photo courtesy of Steve McCaw)



Jennie Foushee joked with Birnbaum as the fourth annual Friends and Family Day officially began. Debuting in Rodbell Auditorium in 2006, the next year the event moved outdoors in a big way. (Photo courtesy of Steve McCaw)



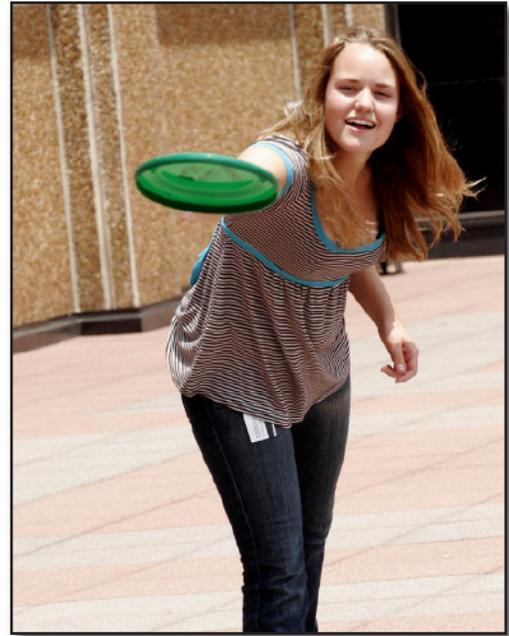
For younger employees, such as Postdoctoral Fellow Jeffrey Sunman, center, the event was also "Bring Your Toddler to Work" day. In the background, Mitch Williams also watched the games. (Photo courtesy of Steve McCaw)



Resting on their laurels at least for the time being, the OM Blazin' Bullets relaxed after their decisive win. Standing, from left, were Chuck Watkins, Lakesia Register, Marc Hollander, William Johnson, Scott Capouch, Wesley Averette, Craig Everett, Chad Emory, April Parker, William Ragland and Stephanie Bullock-Allen. Kneeling, from left, were VeeVee Shropshire, Rick Weaver, Kyle Hawkins. Seated on the grass, from left, were Charletta Fowler, Terry Wills and Derrick Vest. (Photo courtesy of Steve McCaw)



VeeVee Shropshire showed off her vocal talent as she got into the karaoke spirit. (Photo courtesy of Steve McCaw)



Summers of Discovery intern Madeline Rooney looked right at home throwing a Frisbee on the patio. (Photo courtesy of Steve McCaw)



The inflatable slide and mechanical bull set up on the lawn beside the lake were really intended for kids, but the grownups also found them irresistible. (Photo courtesy of Steve McCaw)



Still, once the grownups gave an inch, the kids were back where they deserved to be — at the center of the playground action. (Photo courtesy of Steve McCaw)

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Staff Mingle at Keystone's Beach Party

By Robin Mackar

In a second major effort to give NIEHS staff in the Keystone Building a lunchtime opportunity to get to know their neighbors better, volunteers from the three floors organized a beach-themed cookout on June 4. The "Wish I Were at the Beach" event proved to be even more popular than the building's inaugural "Keystone 2009 Meet and Greet Tea Party," held January 26.

"These events provide an opportunity for staff from throughout Keystone to get to know each other better, and share food and fun with people from the different floors and divisions," said Judy Hanson from *Environmental Health Perspectives (EHP)*, who helped organize the event.

Approximately 200 people participated in the afternoon social, with many showing up in beach shirts and toting lawn chairs to mingle with their colleagues under the tents pitched on the grassy area on the side of the 530 Davis Drive building. Attendees were treated to the sounds of the "2 Brass Squared" Band comprised of Dick Sloane from the office of Employee Services, Mike Humble from the Division of Extramural Research and Training, Roger Callahan from the Facilities Operations Branch and retired NIEHS staffer Doug Bristol.

Everyone indulged in grilled burgers, hot dogs and veggie burgers cooked to perfection by Rob Levine of the Computer Training Branch and Tommy Hardee from the Office of Acquisitions. A wide array of salads, sides, snacks, drinks and the typical over abundance of desserts were also available.

"The turnout for this event was terrific," said Dona McNeill, manager of Employee Services and a lead organizer for the event. "Staff really pulled together to make it happen, and we keep hearing from people who hope we can do more of these events."

The volunteers who organized the event, including Molly Vallant, Denise Lasko, Diane Spencer, Martha Barnes, Charlie Tate, Robin Mackar, Judy Hanson, Jackie Osgood, JoAnn Sutthill, Alma Britton, A'tondra Carrie, Jenn Evans, Cynthia Radford, Dona McNeil and Richard A Sloane, were praised and thanked by colleagues from throughout the building.

"Such great team building events wouldn't occur without such volunteerism, and they go a long way to boosting morale," said Nigel Walker, Ph.D., of the National Toxicology Program, whose comment echoed those by others in the Institute.

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



Trombonist Dick Sloane was dressed for the occasion with a straw hat and loose shirt. Everything about him proclaims that it's "summertime, and the living is easy."
(Photo courtesy of Steve McCaw)



Scott Mastin braved an unforgiving sun as he landed his croquet mallet squarely on the ball.
(Photo courtesy of Steve McCaw)



Good friends Molly Vallant, left, and Cynthia Smith share a lighter moment under the shade of trees adjacent to the building. (Photo courtesy of Steve McCaw)



Cynthia Radford helped turn the event into a family affair as she posed with her grandchildren. (Photo courtesy of Steve McCaw)



If he'd lose the company cap, trumpeter Mike Humble — with his mellow shades and cool demeanor — could pass for a musician on break at a real jazz festival. (Photo courtesy of Steve McCaw)



Hard working chefs Rob Levine, left, and Tom Hardee engaged in a little horseplay as they fed ravenous carnivores and selective vegetarians alike. (Photo courtesy of Steve McCaw)



Helen Cuny, left, and Jane Lambert took a well-deserved break from their work supporting the NIEHS Institutional Review Board to enjoy the picnic. (Photo courtesy of Steve McCaw)



Whatever Craig Wladyka, left, and Heather Nichols were discussing over lunch, it probably wasn't information technology. (Photo courtesy of Steve McCaw)

NIH-Hosted Panel Addresses GLBT Health Disparities

By Eddy Ball

As part of its annual “Noons in June” series recognizing Gay, Lesbian, Bisexual and Transgender (GLBT) Pride Month, NIH hosted a panel discussion on June 17 on “Addressing Health Disparities in GLBT Populations” at Lister Hill Auditorium on the NIH campus in Bethesda, Md. NIH made the presentations available for remote viewing via [webcast](#).

The event, which was sponsored by the NIH Office of Equal Opportunity and Diversity Management (OEODM) and [Salutaris](#) — the NIH GLBT Employees’ Forum — opened with a welcome from NIH Acting Director Raynard Kington, M.D., Ph.D.

In his remarks, Kington recalled the 40th anniversary of the Stonewall uprising in 1969 that began the GLBT rights movement and described the legacy of Stonewall and other civil rights movements of the time. “I personally benefited,” he said, “as so many people came together to refuse to tolerate the inequities that existed and then worked so tirelessly for social justice for all.” He thanked the event sponsors for helping to raise awareness of the work yet to be done in pursuit of equal opportunity.

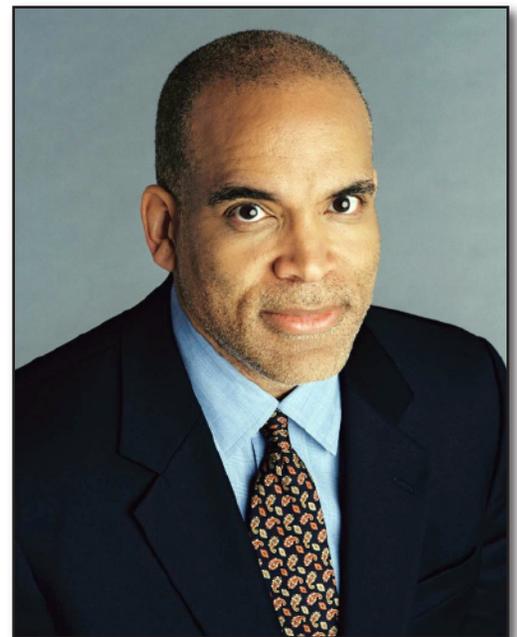
Chair of Salutaris and event moderator Justin Hentges next introduced the event’s panelists — Boston University School of Public Health Professor [Deborah Bowen, Ph.D.](#), University of Illinois at Chicago Professor of Community Health Sciences [Jesus Ramirez-Valles, Ph.D.](#), and University of Pittsburgh Department of Behavioral and Community Health Sciences Professor and Chair [Ronald D. Stall, Ph.D.](#) The speakers, who are NIH grantees, then spent 15 minutes each describing their work in the field of sexual minority health disparity and the problems that investigators encounter in this emerging area of public health research.

Bowen, who studies the higher rates of obesity among lesbians that she argues are linked to sexual orientation, proposed that the “GLBT health disparity movement should think of itself in terms of all other kinds of health disparity.” She identified the paucity of demographic data about sexual orientation as a problem that still hampers investigators who pursue grant support. “To get funding, you have to have evidence that you have a problem,” she explained. “If we don’t have these data published, we’re not on the radar screen.”

Ramirez-Valles focused on the role played by what he called “internalized stigmatization” by GLBT people in creating health disparities. “These GLBT health disparities are not innate,” he said. “They are socially constructed” around notions of gender conformity. He added that when GLBT people “see themselves through the



Hentges is a budget analyst at the National Institute of Dental and Craniofacial Research (NIDCR). (Photo courtesy of NIH)



NIH Acting Director Raynard Kington expressed NIH support for Salutaris and commitment to equal employment and healthcare opportunity for members of the GLBT community. (Photo courtesy of NIH)

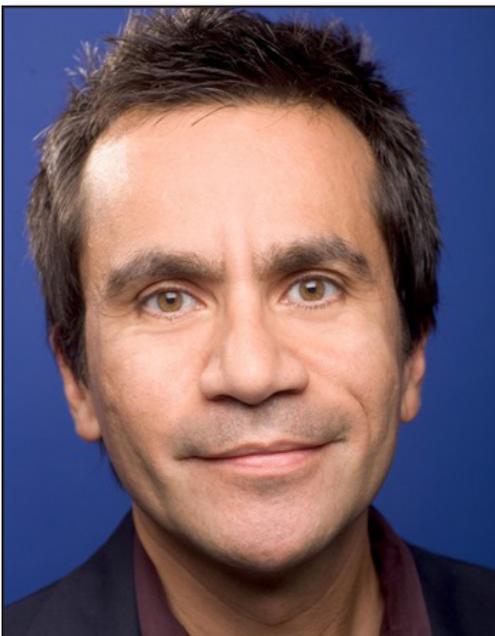
negative lenses of society,” they are more prone to experience substance abuse, unsafe sexual behavior and increased exposure to sexually transmitted diseases. “We need to think about ways to bring the individual and the society together to investigate these health disparities” and impact the problem through cultural and institutional change, he concluded.

In his presentation, Stall pointed to “substantial and life-threatening health risks among gay men that go beyond HIV/AIDS,” including the documented higher rates of smoking among gay men and suspected increased risk for cardiovascular diseases and cancer. He discussed his work developing a graduate-level public health training program in GLBT health issues at the University of Pittsburgh that is helping prepare the next generation of researchers and creating a model for programs at other institutions.

The discussion concluded with a question-and-answer session and final remarks by Hentges, who presented the panelists with tokens of appreciation from NIH and Salutaris.



Bowen applauded the growth of NIH support for GLBT health disparity research, but she also noted, “We’re still in the dating phase of our relationship.” (Photo courtesy of Deborah Bowen)



Ramirez-Valles noted that many questions remain about the long-range impact of GLBT health disparities. He said, “We are seeing the first generation of aging [self-identified] gay people.” (Photo courtesy of Jesus Ramirez-Valles)



Stall, above, and Bowen serve on NIH review sections. Stall called for creation of “an NIH office to advocate for research in this area.” (Photo courtesy of Ronald Stall)

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