



# Environmental Factor

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July 2010

## NIEHS Spotlight



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### [Reid Named Education Outreach Specialist](#)

NIEHS energized its commitment to science education outreach with the appointment of Ericka Reid, Ph.D., who assumed the duties of education outreach specialist in June.

## Science Notebook



### [Non-coding RNAs: What To Be or Not To Be](#)



Guest lecturer John Rinn, Ph.D., explored the role of large non-coding RNAs in establishing the distinct epigenetic states of cells and their misregulation in cancer.



### [Arsenic Exposure Shown to Increase Risk of Death](#)



According to a new NIEHS-funded study by Superfund researchers, 35-77 million Bangladeshis may face a higher risk of death from chronic exposure to arsenic in water.



### [Pollution Linked to Severity of Sleep-Disordered Breathing](#)

A new study by Harvard researchers, funded in part by NIEHS, found the first link between air pollution exposure and SDB, a known cause of cardiovascular disorders.



### [Identifying Environmental Carcinogens Through Epidemiology](#)

During his June 17 visit, Paolo Boffetta, M.D., focused on identifying environmental risk factors that lead to cancer, a challenge that is central to the mission of NIEHS.



### [Discovery May Open Doors for New Blood Pressure Treatments](#)

NIEHS-funded researchers have found that increasing certain proteins in the vessels of mice relaxed the vessels and lowered blood pressure.

## NIEHS Spotlight



### [Candidates Interview for NIEHS Toxicology Liaison](#)

Because toxicological studies are vital to understanding how the environment influences human disease, the person who serves as the NIEHS toxicology liaison will play an important role.



### [NIEHS Scientists Attend Endocrine Meeting](#)

A delegation of NIEHS scientists and grantees participated in ENDO 2010: The 92nd Annual Meeting & Expo held June 19–22 in San Diego, Calif.



### [Report on Carcinogens Moves Toward Completion](#)

The 12th Report on Carcinogens came closer to completion during an NTP Board of Scientific Counselors meeting on June 21-22 in Rodbell Auditorium at NIEHS.



### [NTP Hosts International Visitors](#)

NICEATM Director Rear Admiral William Stokes, D.V.M., hosted a visit by representatives from the European Union and the Republic of Korea June 16.



### [Committee Advises on Alternative Toxicological Methods](#)

Maximizing animal care and welfare was one of several topics addressed at the June 17-18 meeting of the Scientific Advisory Committee on Alternative Toxicological Methods



### [Managing Clinical Protocols that Safeguard Human Subjects](#)

On June 7 the NIEHS Office of Human Research Compliance launched a new paperless, integrated web-based system — the Protocol Tracking and Management System.

## Science Notebook



### [Mutations — Raw Materials for Bacterial Evolution](#)

Ivan Matic, Ph.D., a leading molecular geneticist with the French National Institute of Health and Medical Research, visited NIEHS June 7, as a guest of the LMG fellows.



### [Little Things That Do a Lot](#)

The July 7 presentation by Les Hanakahi, Ph.D., “Little Things that Do a Lot: Inositol Polyphosphates in DNA Repair,” was one of the highlights of the 2010 LST seminar program.



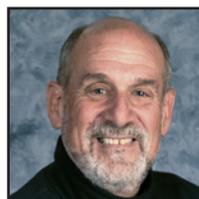
### [Fire Retardant Chemicals Linked to Lower TSH in Pregnancy](#)

According to a new study by NIEHS-funded researchers, exposure to fire retardant chemicals is associated with lower levels of thyroid-stimulating hormone during pregnancy.



### [RSV — Not Just a Children's Disease](#)

“We used to think that respiratory syncytial virus is a cause of runny nose mainly in children,” said grantee Sadis Matalon, Ph.D., during his May 25 talk at NIEHS.



### [30 Year Old Research Still Resonates](#)

Early in his career before joining NIEHS, lab chief David Miller, Ph.D., studied the physiological effects of Louisiana crude oil ingestion on seabirds.



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

The current issue of EHP is sure to spark a lively exchange of opinion with its focus on asbestos, including the commentary “The Case for a Global Ban on Asbestos.”

## NIEHS Spotlight



### [Remembering Superfund Pioneer Dean Carter](#)

Binational programs along the U.S.-Mexico border are helping people on both sides live healthier lives because of the efforts of pioneers such as toxicologist Dean Carter, Ph.D.

## Extramural Research

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

- [Arsenic-Related Mortality in Bangladesh](#)
- [Flame Retardant Linked to Decreased Thyroid Hormone Levels in Pregnant Women](#)
- [Solutions to Arsenic Groundwater Contamination](#)
- [New Kidney Injury Biomarker](#)

## Inside the Institute



### [Ethics Made Easy](#)

During Ethics Day on June 10, the NIEHS Ethics Program showcased its new initiative to help make complying with government ethics regulations easier.



### [Celebrating Friends and Family Day](#)

On this year's Friends and Family Day, sweltering heat curtailed outdoor events, but didn't stop the fun or celebration of Asian and Pacific Islander Heritage.



### [NIEHS — A Pioneer in Sustainability and Green Government](#)

Three NIEHS employees accepted the 2009 Organization Green Champion Award on behalf of the many members of the NIEHS family working for environmental sustainability.



### [Hawk Calls NIEHS Home](#)

On a recent afternoon, photographer Steve McCaw aimed his telephoto lens at a beautiful hawk that apparently is nesting next to the main building on the NIEHS campus in RTP.

## Intramural Research

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

- [A Magnesium-Coordinating Threonine Plays a Critical Role in GTPase Catalysis](#)
- [Cell Survival is Modulated by Phosphorylation of SIRT1](#)
- [Nuclear Receptor CAR Represses the Death of Mouse Primary Hepatocytes](#)
- [Stem Cell Survival Advantage Toward Arsenic Drives Malignant Transformation](#)

## Calendar of Upcoming Events

- **July 6** in Rall D450, 12:00–1:00 p.m. — Receptor Mechanisms Discussion Group Seminar, “Outside-in Signaling via SOCE Is Required for Mouse Egg Activation,” by Carmen Williams, M.D.
- **July 7** in Rodbell Auditorium, 4:00–5:00 p.m. — Presentation on “Rapid Dynamics and Gene Regulation by Nuclear Receptors,” by Gordon Hager, Ph.D.
- **July 8–9** in Rodbell Auditorium, 8:30–5:00 p.m. — EHP-Sponsored Teacher Training Workshop
- **July 8** in Keystone 2164/2166, 12:00–5:30 p.m. — High-Throughput Screening Meeting for Assay Selection Strategy
- **July 9** in Executive Conference Room, 8:00–12:30 p.m. — High-Throughput Screening Meeting for Assay Selection Strategy
- **July 12** in Rodbell Auditorium, 10:00–11:30 a.m. — NIEHS Deputy Director Candidate Lecture by Richard Woychik, Ph.D., “Meeting the Challenges in the Post-Genome Era”
- **July 14** in Rodbell Auditorium, 10:00–11:30 a.m. — NIEHS Deputy Director Candidate Lecture by Steve Kleeberger, Ph.D., topic TBA
- **July 30** in Keystone 2164/2166, 10:00–11:00 a.m. — NTP Biomolecular Screening Branch Seminar, “A High-Throughput Respirometric Assay for Mitochondrial Biogenesis and Toxicity,” by Craig Beeson, Ph.D.

### Summers of Discovery Seminar Series (NIEHS Only)

- **July 6** in Rodbell Auditorium, 10:30–12:00 p.m. — Jennifer Sims, Ph.D., discussing “Heavy Metals”
- **July 13** in Rodbell Auditorium, 10:30–12:00 p.m. — Mercedes Arana, Ph.D., discussing “Radiation”
- **July 20** in Rodbell Auditorium, 10:30–12:00 p.m. — Sophie Bolick, Ph.D., discussing “Hormones and Diet”
- **July 27** in Rodbell Auditorium, 10:30–12:00 p.m. — Amy Abdulovic, Ph.D., discussing “Air Pollution”
- View More Events: [NIEHS Public Calendar](#)

# NIEHS Spotlight

## NIEHS Oil Spill Response Intensifies

By Ed Kang

Two months following the April 20 explosion of the Deepwater Horizon oil rig and the loss of 11 lives, NIEHS continues to expand its role in the response effort. The Institute is widening its focus from developing training and informational resources for the protection of oil spill workers, to identifying the health monitoring and research activities needed to further understand any adverse health effects.

### Protection of oil spill workers paramount

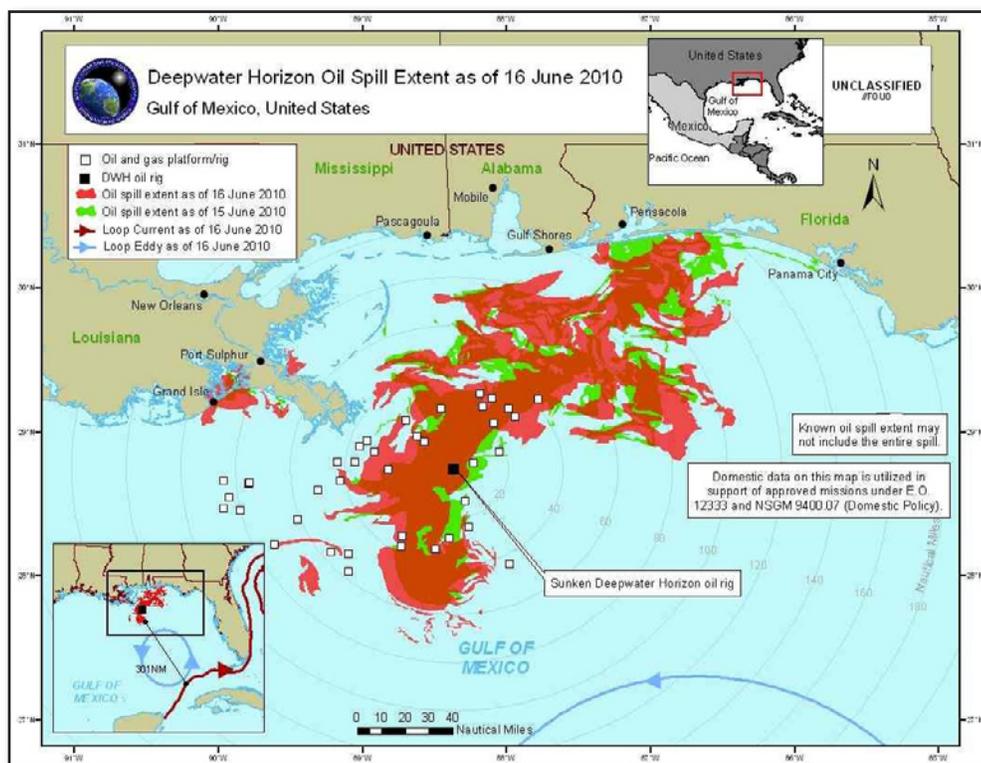
The director of the NIEHS Worker Education and Training Program (WETP), Chip Hughes, and his team have had a continuous presence in the Gulf Coast region since a few days following the explosion, working with multiple partners and other federal agencies to provide worker safety training.

Hughes, who has been the face of NIEHS in the region, described the urgent need for safety and health training for thousands of newly recruited workers. “As professionals and volunteers are mobilized, they need to be aware that they are working around potentially hazardous materials. Training is a critical first step for their protection.”

As of June 10, British Petroleum (BP), the company that owns and operates the failed rig, reported 30,500 people had participated in safety courses that use materials developed and supported by NIEHS WETP. Various levels of training are available including an intensive 40-hour course on Hazardous Waste Operations and Emergency Response,



Miller testified to congressional committees investigating the spill (watch the full [Senate hearing](#)) saying, “One of the most important take-away messages is that there is a clear need for additional health monitoring and research to underpin our collective understanding and public health decisions.”



Map provided by the National Oceanic and Atmospheric Administration (NOAA) shows the extent of the oil spill as of mid-June.

commonly known as HAZWOPER training, and shorter awareness-level courses for those who will have minimal contact with oil spill products. The courses are being provided in English, Spanish, and Vietnamese.

Additionally, more than 5,000 pocket-sized booklets titled “Safety and Health Awareness for Oil Spill Cleanup Workers” have been distributed in multiple languages to instructors, safety officials, front-line responders participating in the British Petroleum Vessels of Opportunity Program, as well as to beach workers in the Shoreline Cleanup Assessment Team.

“The protection of human life is our number one priority and we have been able to provide immediate assistance in the oil spill response,” said Linda Birnbaum, Ph.D., director of NIEHS/NTP. “We must be sure that those doing the work to repair the damage to the Gulf are kept safe.”

### **NIEHS leads research efforts to close knowledge gaps**

In addition to worker education and safety efforts, NIEHS has proactively pursued several avenues to help close knowledge gaps and foster research needed to support science-based public health decisions and actions.

While experts agree there is potential for human health effects, understanding and quantifying these effects requires further study.

“Determination of actual exposure and risk is not a trivial task,” said Aubrey Miller, M.D., senior medical advisor to the director of NIEHS, in statements to the U.S. Senate and House committees investigating the spill. “NIH is exploring a variety of different funding mechanisms and programs to carry out what will be important research related to this particular disaster and the people whose health may be affected by it.”

On June 15, NIH Director Francis Collins, M.D., Ph.D., announced an investment of \$10 million to support NIEHS research on the potential human health effects of the oil spill. A group of clean-up workers and Gulf residents will be recruited, and their health histories and tissue samples will be collected. Researchers will also monitor oil spill workers for respiratory, immunological, and neurobehavioral effects. Information about the nature of their exposures, including any clean-up work performed, will help to establish a valuable baseline of information.

NIEHS has also established a grant program for time-sensitive research and community education to quickly fund research on the public health impact of the oil spill, in addition to its co-funding of the Centers for Oceans

## **Science Workshop Examines Health Issues**

At the request of the U.S. Department of Health and Human Services, the Institute of Medicine (IOM) convened a [public meeting](#) June 22-23 in New Orleans to look at ways to prevent and monitor long-term health impacts of the oil spill. The IOM, the health arm of the National Academy of Sciences, is an independent, nonprofit organization that provides unbiased advice to decision makers and the public — its goal is to improve public health.

Participants from across many federal and state agencies, as well as private and academic institutions, reviewed current knowledge about the human health effects of exposure to oil, weathered oil products, and dispersants, and identified gaps in this knowledge. Researchers identified the populations most at risk for health problems as a result of the oil spill and considered ways to effectively communicate to these groups. Monitoring the spill’s potential negative effects on health and gathering data to further understand the risks to human health were also discussed.

NIEHS representatives in attendance were: Aubrey Miller, M.D., senior medical advisor to the director; James Remington, Worker Education and Training Branch analyst; William Suk, Ph.D., Superfund Hazardous Substances Basic Research and Training Program director; Scott Masten, Ph.D., National Toxicology Program staff scientist; Dale Sandler, Ph.D., Epidemiology Branch chief; and, Chris Portier, Ph.D., NIEHS senior advisor.

and Human Health with the National Science Foundation (NSF). The [Centers](#) have responded by providing expertise to health departments, monitoring beach conditions in real time, and dispatching researchers for water and wildlife sampling and analyses. Additional “rapid response” funds have also been provided by NSF to help carry out these efforts.

And more is on the way, as an Institute of Medicine public meeting June 22-23 made clear ([see text box](#)). NIEHS/NTP Director Linda Birnbaum, Ph.D., told an audience of the NTP Board of Scientific Counselors June 21, “Stay tuned,” as new developments occur almost on a daily basis.

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

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## Grantee Honored for Allergy Research

*By Eddy Ball*

[NIEHS-funded](#) nanoPharma researcher Chris Kepley, Ph.D., was one of two young scientists to receive the prestigious 2010 PhARF (Phadia Allergy Research Forum) Award at a ceremony in London June 7.

Genoa University Professor and PhARF Scientific Committee Chairman Walter Canonica, M.D., presented the award during a special symposium at the 2010 Congress of the [European Academy of Allergology and Clinical Immunology](#). Kepley shares a cash award of \$50,000 with Nikolaos Papadopoulos, M.D., of the University of Athens in Greece. Both winners are invited to hold a speech at Rudbeckdagen, or [Olof Rudbeck Day](#), October 15. Rudbeckdagen is an annual event organized by the Uppsala Physician Society and the area of Medicine and Pharmacy at Uppsala University in Sweden.



*Kepley, left, received his award from Walter Canonica, Chairman of the PhARF Scientific Committee. (Photo courtesy of Chris Kepley)*

Kepley’s research team was the first to show that fullerenes, hollow carbon nanospheres made up of 60 atoms sometimes referred to as buckyballs, are able to block the allergic response in human cell culture experiments and mice. The PhARF Award honors his dedication to finding new ways to turn off the allergic response and his impressive body of leading-edge research in the field.

### Kepley enjoys a high profile in his field

Since 2008, Kepley has been the nanoImmunology group leader in the nanoworks division of Luna Innovations, Inc., developer and manufacturer of new-generation products for the healthcare, telecommunications, energy, and defense markets. Kepley is the principal investigator on an NIEHS grant, “Prevention of Allergic Disease Using Nanomaterials,” managed by Health Scientist Administrator Sri Nadadur, Ph.D.

Prior to joining Luna, Kepley was a professor at the Virginia Commonwealth University School of Medicine. Along with co-chairing symposia and delivering lectures at meetings of the American Academy of Allergy,

Asthma, and Immunology, he currently serves on the Scientific Research Advisory Board for the Food Allergy and Anaphylaxis Network. Kepley also serves on the NIH Bioengineering Sciences & Technologies Integrated Review Groups, the American Recovery Act Limited Competition, and the Congressionally Directed Medical Research Panel.

### **PhARF promotes allergy research**

PhARF was established in 1987 to honor the 20th anniversary of the co-discovery at Uppsala University of IgE, the immunoglobulin that triggers such classic allergic diseases as asthma, hay fever, eczema, and anaphylactic shock. PhARF is sponsored by Phadia, a leading company in the field of *in vitro* allergy diagnostics.

The objective of PhARF is to encourage progress in allergy research through the recognition of a young outstanding investigator by means of an international award. PhARF also serves as a forum for scientific discussion by arranging symposia and workshops. The group cooperates with established scientific organizations in the allergy and immunology area and the Award is presented in connection with the World Allergy Organization and the European Academy of Allergy, Asthma and Immunology.

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## **Olden Honored for Scientific Achievement**

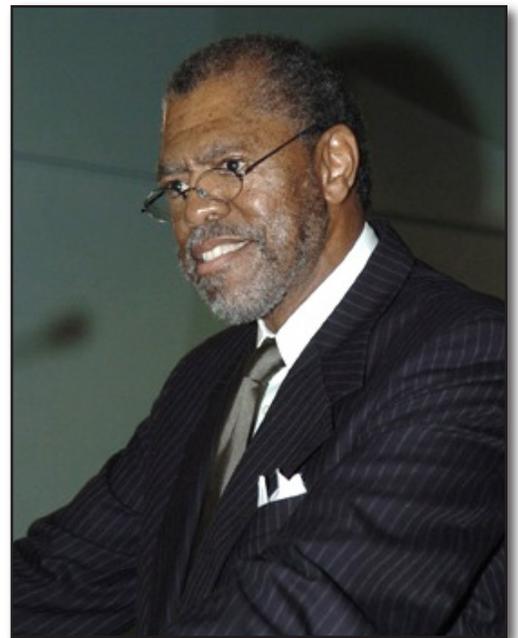
*By Eddy Ball*

[NIEHS Director Emeritus Ken Olden, Ph.D.](#), recently added yet another award to his long list of honors. At the annual gala of the Bronx Community College (BCC) Foundation held at the New York Botanical Garden, Olden was one of five distinguished New Yorkers recognized for their support of a quality educational environment at BCC, according to a June 1 [press release](#) issued by The City University of New York.

At the gala, organized around the theme “Building on a Dream,” Olden received the Robert L. Clarke Award for Scientific Achievement. The award is named for one of BCC’s most beloved chemistry professors.

Olden is founding dean of the new [CUNY School of Public Health](#), the first of its kind school of public health with an urban focus. In 2011, the new program will begin offering graduate programs in its new facility, which celebrated its groundbreaking in November 2009.

Olden served as director of NIEHS/NTP from 1991 to 2005, and he remained at the Institute as principal investigator of the Laboratory of Molecular Carcinogenesis Metastasis Group until he left for New York in September 2008 ([see story](#)).



*Olden, above, shown during a lecture at Harvard University, has said he hopes the CUNY School of Public Health will be “the Mecca, the epicenter for modern public health.” (Photo courtesy of Harvard University)*

Also receiving awards at the event were four other BCC supporters:

- [Allan Dobrin](#), CUNY executive vice chancellor and chief operating officer
- [Van Thompson](#), project manager for the New York office of Skanska USA Buildings, Inc.
- Howard Stein, New York businessman and BCC supporter
- Beverly Spitzer, New York entrepreneur and BCC supporter

Founded in 1957, BCC is the oldest of six community colleges in the CUNY system. Its campus overlooks the Harlem River at University Avenue and West 181st Street. In addition to its 30 associate degree and certificate programs, BCC also has initiatives that are normally not associated with community colleges. These include the National Center for Educational Alliances (NCEA), which is currently collaborating with South African Further Education and Training Colleges, and the Center for Sustainable Energy, which promotes the use of renewable and efficient energy technologies in urban communities.

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## Law and Science Make a Winning Combination

*By Sophie Bolick*

Postdoctoral Fellow Jeff Sunman, Ph.D., begins a new phase of his scientific career as a patent agent with the law firm Alston & Bird, LLP, in Raleigh, after spending five years with the Laboratory of Molecular Carcinogenesis (LMC) [Cell Adhesion Group](#) as a recipient of an NIH Intramural Research Training Award (IRTA).

### Passing the difficult Patent Bar

Sunman recently passed the U.S. patent bar, a complex exam that he credits as a key factor in landing his new position with the law firm. As a patent agent, Sunman will prosecute biotechnology patents for clients before the U.S. Patent and Trademark Office. Many aspiring agents transition into the field of patent law as patent specialists, spending a year studying for the patent bar in order to become registered agents. However, Sunman spent many evenings and weekends during his postdoctoral training studying independently, completing a home study course offered by the Practising Law Institute and researching previously used exam questions.

To acquire the necessary level of familiarity with patent law, Sunman also spent the past few years attending seminars and symposia discussing the fields of intellectual property and biotechnology. He also attended relevant continuing legal education courses on-line during his lunch hours.

### Gaining an edge with patent experience

In addition, Sunman gained valuable hands-on experience during the course of his fellowship when he and Steve Akiyama, Ph.D., head of the Cell Adhesion Group, decided to patent one of his scientific discoveries.



*Sunman's career development story is an example of how valuable focused planning, extra effort, and active networking can be for finding the right non-bench position. (Photo courtesy of Steve McCaw)*

“Jeff very enthusiastically took the lead in coming up with precedents for the Employee Invention Report (EIR) we submitted to the NIEHS Technology Evaluation and Advisory Committee (TEAC), researching patent law to help me defend the EIR before the TEAC, and researching background information to help work out the patent claims with the attorney assigned to our case,” explained Akiyama.

### **A productive research career at the bench**

Not surprisingly, Sunman also made several major contributions to the study of proteases in the tumor microenvironment that regulate integrin-mediated processes such as cell migration. “First, he established a new model system to study the mechanism of P-selectin induced migration of cells out from an artificial tumor mass,” said Akiyama. He also identified a novel mechanism for matrix metalloproteinase-9 in stimulating cell migration independent of its catalytic activity.

During the course of his postdoctoral fellowship, Sunman took advantage of every opportunity to present his research and developed communication skills. He was the recipient of a Fellows Award for Research Excellence (FARE). “He was a very good writer when he came to NIEHS,” Akiyama said, “but he was able to hone his writing skills even more.” Sunman submitted abstracts for NIEHS Science Day and the Annual Fellows Training Conference, presented posters at national meetings, and co-authored a couple of manuscripts.

### **Making additional contributions**

As a member of the NIEHS Trainees Assembly (NTA) Steering Committee, Sunman was an active member of the fellows’ community. He served on numerous LMC committees and helped train other researchers within the Cell Adhesion Group. Akiyama calls him “the ultimate team player.” He continues, “I am very happy Jeff has found a position that, I think, plays to his greatest strength.”

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

## **Using the NIEHS Annual Career Fair to Network**

Sunman was a member of the 2010 NIEHS Career Fair Planning Committee, responsible for organizing and moderating the panel discussion focused on patent law careers. “Networking was critical to getting the interview in the first place,” stated Sunman when asked about his job search.

Sunman had met Alston & Bird partner [Murray Spruill, J.D., Ph.D.](#), chair of the firm’s Biotechnology and Pharmaceutical Patent Group, at an off-site event some time ago. This positive interaction led to Spruill’s invitation to participate in the Career Fair as a panelist. As a co-chair of this panel, Sunman was able to follow-up with Spruill, who turned out to be the hiring partner for the patent agent position posted a few months ago.

A discussion with other fellows interested in patent law at last year’s NIEHS Career Fair led Sunman to create the LinkedIn “Patent Law Study and Transition Group.” This group is a valuable resource for scientists and engineers preparing to transition to a career in patent law and currently has more than 130 members worldwide.

Sunman made new contacts by networking through this group and relied on several members for advice when it came time to interview for his new position. He credits these professional contacts with insight that “allowed me to ask better questions about the firm and the position.”

See stories about NIEHS Biomedical Career Fairs in [2010](#), [2009](#), [2008](#), and [2007](#) and Sunman’s [FARE](#) award.

# Reid Named Education Outreach Specialist

By Eddy Ball

NIEHS energized its commitment to science education outreach with the appointment of Ericka Reid, Ph.D., who assumed the duties of education outreach specialist in June. Reid will coordinate local efforts across the Institute's divisions and serve as the central liaison to other programs and educational institutions nationwide in the development of innovative science education and programs for under-represented populations.

With her training in education and counseling, as well as her extensive background in higher education recruitment and retention programs, Reid brings an experienced approach to education outreach efforts at NIEHS.

## Education and experience

Reid received her Ph.D. in educational psychology with an emphasis on women and minorities in science, technology, engineering, and mathematics (STEM) from Georgia State University in Atlanta and her M.Ed. in counseling and development with a concentration in student development in higher education from the University of North Carolina at Greensboro.

Immediately following her master's program, Reid worked for the University of Tennessee Educational Advancement Program and Pellissippi State Technical Community College Student Development Center in Knoxville, Tenn.

For the past 12 years, Reid lived and worked in Atlanta, Ga. She served with a variety of organizations and higher education institutions, including the Advanced Academy for Future Teachers at Georgia State University, where she completed her doctorate, Emory University Center for Behavioral Neuroscience, and Spelman College Office of Graduate School Relations.

Most recently Reid served as the manager of professional development for the American Society of Heating, Refrigerating, and Air-Conditioning Engineers (ASHRAE), an international membership association, where she was responsible for the development of and recruitment for continuing education courses.

## A part of the NIEHS leadership team

Looking ahead to the opportunities and challenges of her new position, Reid said she is proud to be a part of the NIEHS family and working toward realizing one of its important initiatives.

"It's an honor to be part of an organization and team that actively engages in making science education and career opportunities available to those who have been historically overlooked or underserved," Reid said. "I look forward to working with colleagues who so clearly understand the importance of broad perspectives and the value of inclusion."

Reid assumes a leadership role filled for 14 years by former NIEHS Director of Education and Biomedical Research Marian Johnson-Thompson, Ph.D., who retired in September 2008 ([see story](#)). Following her appointment as NIEHS/NTP director in 2009, Linda Birnbaum, Ph.D., made reinvigorating education outreach a top priority as she began the process of recruiting permanent members of her new leadership team.



*As one of the finalists for the position, Reid, above, spoke March 18 on the topic "Addressing the Under-Representation of Women and Minorities in STEM Disciplines." (Photo courtesy of Steve McCaw)*

# Candidates Interview for NIEHS Toxicology Liaison

By Robin Arnette

The search for the new toxicology liaison recently culminated with two of the candidates giving talks at NIEHS. During their visit, both scientists met with several staff members and toured the Institute. The position is based at the NIEHS office in Bethesda, Md.

Because toxicological studies are vital to understanding how the environment influences the development and progression of human disease, the person who serves as the NIEHS toxicology liaison will play an important role. The toxicology liaison will provide a valuable link between NIEHS and other federal research and regulatory programs, industries, labor, and a wide variety of constituency and advocacy groups.

## The finalists

- Linda Youngman, Ph.D., presented “Human Clinical Trials and Animal Research – Applied Toxicology” on June 15. Youngman is a scientist/investigator in the Office of Research Integrity at the U.S. Department of Health and Human Services (HHS).
- Christopher Weis, Ph.D., D.A.B.T. presented “Applied Environmental Science: From Laboratories to Trenches” on June 25. Weis is a senior toxicologist at the U.S. Environmental Protection Agency National Enforcement Investigations Center.

The toxicology liaison will serve as a senior advisor to NIEHS/NTP Director Linda Birnbaum, Ph.D., and will also represent the Institute on national and international committees, subcommittees, task forces, and ad hoc working groups. Birnbaum said, “I’m looking forward to working with the new liaison. The post will further the NIEHS mission.”



*Youngman’s talk focused on the different experiences she has had as a toxicologist. She told the audience, “I’ve had a very varied career that hopefully brings a lot of skills to the table.” (Photo courtesy of Steve McCaw)*



*NIEHS Deputy Scientific Director William Schrader, Ph.D., attended both of the talks by candidates for the liaison position. He was one several people in the Institute who have followed the selection process closely. (Photo courtesy of Steve McCaw)*



*Weis described a number of projects he has been involved in that involved toxicological testing. One of the most memorable was the 2001 anthrax scare at the Hart Senate Office Building in Washington, D.C. (Photo courtesy of Steve McCaw)*

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# NIEHS Scientists Attend Endocrine Meeting

*By Robin Arnette*

Several NIEHS scientists and grantees participated in the ENDO 2010: The Endocrine Society's 92nd Annual Meeting & Expo held June 19–22 in San Diego, Calif. The gathering allowed scientists to share their latest findings in research topics such as thyroid cancer, obesity, endocrine disruptors, diabetes, growth hormones, and sex steroids.

According to Arlyn Riskind, the ENDO 2010 media relations contact, the [meeting](#) attracted over 7,000 researchers and journalists and featured 2,199 poster and 264 oral presentations. Several NIEHS postdocs and staff scientists attended the conference along with principal investigators [Ken Korach, Ph.D.](#), [Carmen Williams, M.D., Ph.D.](#), and [John Cidlowski, Ph.D.](#) Cidlowski received the Edwin B. Astwood Award at the [2008 ENDO meeting](#).

[The Endocrine Society](#)<sup>®</sup> boasts a membership of more than 14,000 endocrinologists from all over the globe. Its members include physicians, basic and clinical researchers, clinical and postdoctoral fellows, students and more. Next year's meeting will be held on June 4–7, 2011 in Boston, Mass.

## NIEHS ENDO 2010 Abstracts

The NIEHS scientists and grantees had a combined total of 17 oral and poster presentations at ENDO 2010:

- Sexually Dimorphic Actions of Glucocorticoids: A Potential Link to Gender Prevalent Inflammatory Diseases — D Duma, JA Cidlowski — Poster Presentation
- Anti-Apoptotic Actions of Glucocorticoid in Cardiomyocytes — R Ren, JA Cidlowski — Poster Presentation
- GEMS (Gene Expression MetaSignatures), a Web Resource for Querying Meta-Analysis of Expression Microarray Datasets: Dihydrotestosterone in LNCaP Cells — SA Ochsner, CM Watkins, ES Chen, DL Steffen, B Risek, IU Agoulnik, NL Weigel, WT Schrader, NJ McKenna — Poster Presentation
- Neonatal Genistein Exposure Permanently Disrupts Female Reproductive Tract Gene Expression and Tissue Architecture During Pregnancy — WN Jefferson, SM Wagner, E Padilla-Banks, CJ Williams — Poster Presentation
- The Extranuclear Estrogen Receptor Improves Pancreatic Islet Lipid Homeostasis — JP Tiano, C Le May, KS Korach, F Mauvais-Jarvis — Oral Presentation
- Characterizing the In Vivo Physiological Roles for ER AF-1 and AF-2 Using a Mutant AF-2 Knock-In Mouse Line — Y Aro, K Hamilton, M Ray, G Scott, KS Korach — Poster Presentation
- The Human Glucocorticoid Receptor Single Nucleotide Polymorphism GR9A3669G Alters Gene Expression — CM Jewell, JA Cidlowski — Poster Presentation
- Epigenetic Regulation of Cyclic-Nucleotide-Mediated Signaling in Rat Neonatally Exposed to Bisphenol A (BPA) — W Tang, X Zhang, J Chen, S Karyala, L Morey, YY Cheung, M Medvedovic, GS Prins, S Ho — Oral Presentation
- Progesterone Alters Tumor Cell Composition, Increases Tumor Cell Proliferation and Survival, and Promotes Invasive Behavior in Carcinogen-Induced Mammary Cancer in the Rat — A Kariagina, AN Kramer, KN Miller, SZ Haslam — Oral Presentation

- Gold Nanoparticles Alter Progesterone and Estradiol-17 Beta Accumulation *In Vitro* in a Rat Ovary Culture Model — JK Larson, MJ Carvan III, R Klaper, RJ Hutz — Poster Presentation
- Hepatic Enzyme Inducers Increase Thyroxine (T4) Catabolism in Human and Rat Hepatocytes — VM Richardson, MJ DeVito — Poster Presentation
- Dioxin Disrupts Reproductive Function over Multiple Generations — KG Osteen — Symposia
- Triclocarban Modulates Cytokines *In Vitro* — NC Olsen, J Chen, AJ Duleba, BL Lasley — Poster Presentation
- Glucocorticoid Regulation of Gene Expression in Uterine Leiomyomas — SD Whirledge, D Dixon, JA Cidlowski — Poster Presentation
- Low-Doses of BPA and Estrogen Increase Ventricular Tachycardia and Fibrillation Following Ischemia-Reperfusion in the Female Heart — S Yan, W Song, SM Belcher, H-S Wang — Poster Presentation
- Alterations in Mammary Gland Function and Reproductive Capacity in CD-1 Mice Exposed Perinatally to Bisphenol-A — PR Wadia, NJ Cabaton, MV Maffini, BS Rubin, C Sonnenschein, AM Soto — Oral Presentation
- Extranuclear Actions of Estrogen in the Vasculature — PW Shaul — Symposia
- Identification of Hormone-Induced Bioactive Mitochondrial Protein Complexes in MA-10 Leydig Cells — MB Rone, G Rammouz, J Blonder, DA Prieto, T Veenstra, V Papadopoulos — Poster Presentation



NIEHS employees staffed the Institute's exhibit and booth at ENDO 2010. (Photo courtesy of Rita Hanson)

# Report on Carcinogens Moves Toward Completion

By Thaddeus Schug

The [12th Report on Carcinogens \(RoC\)](#) came closer to completion during an NTP Board of Scientific Counselors (BSC) meeting on June 21-22 in Rodbell Auditorium. NTP scientists presented draft substance reports for the final three compounds being considered for possible listing in the report for BSC consideration and public comment, including glass wool fibers used in insulation and filtering systems, cobalt-tungsten carbide — powders and hard metals found in cutting tools — and formaldehyde, a widely used chemical found in resins and plastics and used for medical preservation.

Along with other business ([see text box](#)), the BSC heard a Center for the Evaluation and Risk to Human Reproduction (CERHR) proposal for a literature review of the potential health effects of exposure to cancer chemotherapy *in utero*.

## 12th Report on Carcinogens

Mary Wolfe, Ph.D., director of the NTP Office of Liaison, Policy and Review, opened the presentations with an overview of the [multi-step scientific review process](#) used for the RoC. Wolfe explained, “Each phase of the review process offers opportunities for public input and scientific deliberation” ([see 2009 story](#)). She added that “the board is charged with determining whether the scientific information cited in each draft substance profile is technically correct, clearly stated, and supports the NTP’s preliminary decision regarding its listing in the RoC.” The NTP will review BSC and public comments before recommending final classifications for the substances for the 12th RoC.

The NTP recommended retaining glass wool fibers listing as “reasonably anticipated to be a human carcinogen” as reported in the 11th RoC, despite objection by the North American Insulation Manufacturers Association (NAIMA) and several other public stakeholders, and the findings of its 2009 expert panel ([see story](#)). NAIMA representatives argued that NTP should follow the recommendations of its independent expert panel and separate glass wool into different categories according to specific criteria related to their size and durability.



*NIEHS/NTP Director Linda Birnbaum smiled at her audience during a lighter moment following her briefing to the BSC on the Institute’s extensive and growing response to the Gulf oil spill and commitment to global environmental health. Birnbaum has assembled a team of scientists, led by NIEHS Senior Medical Advisor Aubrey Miller, M.D., to coordinate response efforts with other federal agencies. (Photo courtesy of Steve McCaw)*



*NTP Associate Director John Bucher, Ph.D., left, and BSC Chair Raymond Novak, Ph.D., looked on during Howdeshell’s concept proposal for evaluating cancer chemotherapy during pregnancy. (Photo courtesy of Steve McCaw)*

In response, NTP's Gloria Jahnke, D.V.M, noted, "Although not all glass fibers are carcinogenic, there is sufficient evidence from studies in experimental animals and mechanistic data to group them as one class." NTP scientists also pointed to the lack of any clear scientifically established way to distinguish between those fibers that cause cancer and those that do not without testing each individual product.

Discourse was also animated over NTP's recommendation to reclassify formaldehyde from a "reasonably anticipated carcinogen" to a "known human carcinogen" (see [2009 expert panel story](#)). NTP RoC Center Director Ruth Lunn, Dr.P.H., said, "The decision to change the listing status of formaldehyde is based on sufficient evidence in human epidemiology studies with supporting mechanistic information." Much discussion centered over recent studies linking formaldehyde exposure to forms of leukemia, in addition to less common cancers of the nasopharynx and sinonasal cavity.

Lunn also presented evidence in support of listing cobalt-tungsten carbide: powders and hard metals as "reasonably anticipated to be human carcinogens."

### **CERHR proposes evaluation concept**

Also during the day and a half meeting, Kembra Howdeshell, Ph.D., presented a CERHR concept to evaluate literature concerning the pregnancy outcomes of women treated with cancer chemotherapy during pregnancy and follow-up on their offspring exposed *in utero*. According to Howdeshell, a growing number of women are being diagnosed with cancer during pregnancy. Estimates range from 1 in 1,000 to 1 in 6,000. Treatment most often involves some form of chemotherapy. However, nearly all chemotherapy agents are U.S. Food and Drug Administration Pregnancy Category D, which investigational or post-marketing data show risk to the fetus. The evidence of risk of the chemotherapeutic agents usually comes from studies in laboratory animals.

Howdeshell's proposal is for the NTP to develop a monograph, which "will provide a thorough survey and critical scientific evaluation of the human literature, to determine whether cancer chemotherapy administered during pregnancy affects pregnancy outcomes." Howdeshell added, "It should provide physicians and their patients with an informed perspective on what is known about the developmental effects following exposure to chemotherapeutic agents *in utero*."

## **Additional NTP Board of Scientific Councilors Meeting Highlights**

- NIEHS/NTP Director Linda Birnbaum, Ph.D., briefed BSC on NIEHS response to gulf oil spill.
- NTP CEBS Scientific Administrator Jennifer Fostel, Ph.D., demonstrated the Chemical Effects in Biological Systems (CEBS) data management system to the BSC.
- NTP Associate Director John Bucher, Ph.D., provided updates on finance, staffing, and scientific events at NTP.
- NTP Toxicologist Barry McIntyre, Ph.D., presented a research concept for Hydroxyurea.



*BSC member Elaine Faustman, Ph.D., engaged in the debate over classification of glass wool fibers. The BSC spent a significant amount of time questioning NTP scientists and public stakeholders on the differences between longer, less soluble "special wool fibers" used in filtering systems, and glass wool fibers used in insulation products. (Photo courtesy of Steve McCaw)*



*NTP BSC member David Eastmond, Ph.D. reads his review of the NTP draft substance profile for formaldehyde. Many of Eastmond's comments dealt with the scientific evidence linking formaldehyde exposure to leukemia. (Photo courtesy of Steve McCaw)*



*Lunn, right, and Bucher, left, listened to BSC comments on formaldehyde, which was one of three chemicals reviewed at this meeting. (Photo courtesy of Steve McCaw)*

(Thaddeus Schug, Ph.D., is a postdoctoral research fellow in the NIEHS Laboratory of Signal Transduction and a regular contributor to the Environmental Factor.)

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## NTP Hosts International Visitors

*By Debbie McCarley*

Rear Admiral William Stokes, D.V.M., director of the [NTP Interagency Center for the Evaluation of Alternative Toxicological Methods \(NICEATM\)](#), hosted a visit by representatives from the European Union and the Republic of Korea June 16. The meetings fostered discussion of progress on international efforts to reduce the number of animals required for product safety testing and to develop internationally consistent regulations and guidelines for more human toxicological methods.

The meeting provided an opportunity for the participants to review the progress of ongoing international validation studies evaluating new non-animal test methods to identify potential hazards. In addition to discussing the progress of ongoing validation studies, the international visitors attended the annual meeting of the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) at the U.S. Environmental Protection Agency Research Triangle Park campus June 17 and 18 ([see story](#)).

Joachim Kreysa, Ph.D., head of the European Centre for the Validation of Alternative Methods (ECVAM), attended the international meeting. ECVAM is a unit of the Joint Research Centre within the European Commission's Institute for Health and Consumer Protection.



*Kreysa, left, and Stokes posed outside NTP offices during the international visitors' meetings with the agency's scientists. The two faced a very busy next two days with the SACATM meeting at nearby EPA. (Photo courtesy of Steve McCaw)*

Two representatives of the Korean Center for the Validation of Alternative Methods (KoCVAM) also attended — Soon Young Han, Ph.D., director of KoCVAM, and Chea-Hyung Lim, D.V.M. KoCVAM is part of the National Institute of Food and Drug Safety in the Korean Food and Drug Administration. Han and Lim also met with NTP Associate Director John Bucher, Ph.D., and other NIEHS scientists.

Stokes was a featured speaker at the symposium celebrating establishment of KoCVAM last year. Hajime Kojima, Ph.D., director of the Japanese Center for the Evaluation of Alternative Methods (JaCVAM) provided a written update on Japanese activities that was presented at the meeting.

ECVAM and JaCVAM are participants in the International Cooperation on Alternative Test Methods (ICATM), through which the ongoing validation studies are being coordinated. ICATM was established last year as the result of efforts initiated by NICEATM and the [Interagency Coordinating Committee on the Validation of Alternative Methods \(ICCVAM\)](#), an interagency committee of the U.S. federal government administered by NICEATM.

The ICATM agreement provides a framework through which NICEATM and ICCVAM can cooperate with other international validation organizations to speed the international acceptance of scientifically valid test methods that may reduce, refine, or replace animal use while continuing to protect people, animals, and the environment. Representatives of NICEATM and ICCVAM, ECVAM, JaCVAM, and Health Canada signed the ICATM agreement. KoCVAM has expressed interest in joining ICATM.

The ICATM agreement facilitates activities such as the ongoing validation studies led by NICEATM. These studies are evaluating test methods to identify potential endocrine disruptors and were designed by NICEATM in consultation with ICATM participants. Laboratories in Japan and Korea, sponsored by JaCVAM and KoCVAM, are participating in the studies to ensure the test methods yield consistent results when conducted by different laboratories.

ECVAM, JaCVAM, Health Canada, and KoCVAM will have an opportunity to nominate experts to participate on a NICEATM-ICCVAM-sponsored peer review panel that will be convened in 2011 to review the data from the validation studies and the draft ICCVAM recommendations on the use of the test methods. Following the peer review, ICCVAM will develop final recommendations for U.S. federal agencies. These recommendations will consider the results of the peer review and public comments, as well as comments from the advisory committee and from other ICATM participants.

Active participation of ICATM members throughout the validation study, peer review, and development of final recommendations increases the likelihood that the ICCVAM recommendations will be used to develop internationally consistent regulations and guidelines. Similar international cooperation led to the recent international acceptance of test methods recommended by ICCVAM that identify eye irritation hazards and substances that may cause allergic contact dermatitis.

(Debbie McCarley is a special assistant in National Toxicology Program office.)

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## Guide to Acronyms (in order of appearance)

- **NICEATM** — NTP Interagency Center for the Evaluation of Alternative Toxicological Methods
- **ECVAM** — European Centre for the Validation of Alternative Methods
- **KoCVAM** — Korean Center for the Validation of Alternative Methods
- **JaCVAM** — Japanese Center for the Evaluation of Alternative Methods
- **SACATM** — Scientific Advisory Committee on Alternative Toxicological Methods
- **ICATM** — International Cooperation on Alternative Test Methods
- **ICCVAM** — Interagency Coordinating Committee on the Validation of Alternative Methods

# Committee Advises on Alternative Toxicological Methods

By Robin Mackar

Maximizing animal care and welfare, increasing awareness about alternative toxicological methods, vaccine potency testing, validation issues, and hearing updates on federal and international acceptance of alternative methods were just a few of the topics covered at the June 17-18 meeting of the [Scientific Advisory Committee on Alternative Toxicological Methods Meeting \(SACATM\)](#) held on the U.S. Environmental Protection Agency (EPA) campus in Research Triangle Park, N.C.

NIEHS/NTP Director Linda Birnbaum, Ph.D., provided a warm welcome to all, especially to the international partners in attendance, including Joachim Kreysa, Ph.D., of the European Centre for the Validation of Alternative Methods (ECVAM), Soon Young Han, Ph.D., director of the newly established Korean Center for the Validation of Alternative Methods (KoCVAM) and David Blakely, Ph.D., of Health Canada, who joined the meeting by teleconference. Birnbaum praised the [Interagency Coordinating Committee on the Validation of Alternative Methods \(ICCVAM\)](#) and the [NTP Interagency Center for the Evaluation of Alternative Toxicological Methods \(NICEATM\)](#) for their progress, highlighting the endorsement or adoption of 33 new alternative methods. She also mentioned that she just forwarded two of the first “green technology” ICCVAM test method recommendations to federal agencies for their approval.



*Bucher and Birnbaum listened and responded to discussions at the two-day SACATM meeting. (Photo courtesy of Steve McCaw)*

## Updates and discussion

William Stokes, D.V.M., provided an update on activities. He drew attention to a new publication [The Biennial Progress Report 2008–2009: Interagency Coordinating Committee on the Validation of Alternative Methods](#) which describes ICCVAM activities, test method recommendations, and other progress made during the reporting period. He highlighted some key accomplishments and spoke about upcoming workshops of interest, including the “International Workshop on Alternative Methods to Reduce, Refine, and Replace the Use of Animals in Vaccine Potency and Safety Testing: State of the Science and Future Directions” to be held in Bethesda, Md. September 14-16.

Stokes queried SACATM on the topics of outreach, industry participation, and how to address some regulatory responses to methods. The group had many ideas to share about how to create more awareness for study directors and [Institutional Animal Care and Use Committees \(IACUC\)](#) to make sure they consider alternative methods.



*Warren Casey, Ph.D., the new deputy director for NICEATM, listened carefully to discussions. Casey presented on the validation of endocrine disruptor test methods the first afternoon of the meeting. (Photo courtesy of Steve McCaw)*

SACATM member Karen Brown, Ph.D., began the discussion by saying outreach efforts need to be expanded beyond the toxicology community to other groups, including industry. “Regulatory agencies and industry have to work together,” said Brown. She suggested inviting industry representatives to workshops and presentations to hear about the savings in time, money, and labor that alternative testing methods can often provide.

Marion F. Ehrich, Ph.D., Sharon Meyer, Ph.D., Linda A. Toth, D.V.M., Ph.D., and others suggested more be done to reach out to laboratory animal veterinarians and personnel. They suggested placing articles in publications that lab technicians read such as Nature’s “Lab Animal” as a way to increase awareness about alternative testing methods, as well as getting more concise, yet comprehensive articles into the peer-reviewed literature.

Participants also offered ideas for expanding training grants and other NIH grant mechanisms. George Corcoran, Ph.D., suggested providing travel funds for IACUC members to attend more meetings and workshops.

Helen Diggs, D.V.M., proposed using new media to help create awareness and training for study directors and IACUC members. “I suggest developing Web-based or other training programs that people can access at their leisure,” Diggs said. “These are very busy people who don’t have time or money to travel to hear about the newest methods.”

Members also offered ideas for encouraging industry to submit testing data to NICEATM and providing data for proprietary products from companies without revealing the product identity.



*Brown, left, and Corcoran had much to offer on a wide variety of topics at the recent SACATM meeting. (Photo courtesy of Steve McCaw)*



*SACATM members Diggs, left, and Ehrich engaged in discussions about creating more awareness about alternative toxicological methods. (Photo courtesy of Steve McCaw)*

## Assessment of Acute and Chronic Pain in Animals

A thoughtful and engaging talk, filled with real life practical guidance by veterinary anesthesiologist Alicia Karas, D.V.M., from Tufts University on the first morning of the meeting, set the stage for discussions throughout the meeting. Her talk “Assessment of Acute and Chronic Pain in Animals” was a follow-up to a presentation made at last year’s SACATM meeting by the chair of the [National Research Council Report on Recognition and Alleviation of Pain in Laboratory Animals](#). Karas is one of a handful of experts actively pursuing research in this area.

Karas explained that you have to know something about what an animal’s normal behaviors are, such as their eating, sleeping, nest-building, drinking, fighting and grooming habits. She showed short video clips of mice and rats behaving normally. She also talked about how to use behavioral cues such as changes in movement, nesting, food and water consumption, lack of grooming, posture, and things like weight loss to determine if an animal could be experiencing pain.

“Any large scale, robust measure to assess pain and distress must be simple and involve short observation periods,” was one of the take home messages Karas left with the group.



*International guests from Korea spend some quality time with Birnbaum, center, during the SACATM meeting. Soon Young Han, Ph.D., left, and Chae-Hyung Lim, D.V.M., right, joined Birnbaum during a break in the meeting. (Photo courtesy of Steve McCaw)*



*SACATM Chair, James Freeman, Ph.D., center, led discussion by SACATM members. Seated to his right is Bucher. (Photo courtesy of Steve McCaw)*



*Some of the international collaborators took time from their busy schedule to pose for a picture during their June visit to RTP. Shown, left to right, are Soon Young Han, Birnbaum, Stokes, Joachim Kreysa, and ICCVAM Vice-Chair Jodie Kulpa-Eddy, D.V.M., of the U.S. Department of Agriculture look cool in the hot summer sun. (Photo courtesy of Steve McCaw)*

(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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# Managing Clinical Protocols that Safeguard Human Subjects

By Laura Hall

On June 7, the NIEHS Office of Human Research Compliance (OHRC) launched a new paperless, integrated web-based system — the Protocol Tracking and Management System (PTMS). This system provides an electronic method for the submission, signing, tracking, review, and approval of information related to all NIEHS Institutional Review Board (IRB) activities.

“The IRB’s job is to safeguard the rights and welfare of human subjects by reviewing, approving, and monitoring proposed and continuing research activities involving human subjects within the NIEHS Intramural Research Program,” said Joan Pakenham, Ph.D., director of the NIEHS OHRC. “This system helps manage the process.”

Training of all current NIEHS clinical principal investigators (PIs), study staff, and approving officials occurred during the month of May. New clinical PIs and study staff can receive PTMS training by contacting Andrea Glass, the NIEHS computer support trainer for the PTMS application.

## PTMS Advantages

A major advantage of PTMS is that the IRB staff, approving officials, IRB members, principal investigators, and clinical study staff, can track and manage clinical protocols electronically in real-time — increasing efficiency. This system also allows for the paperless processing and approval of required Personal Financial Holding (PFH) forms by the NIEHS Office of Ethics. PFH forms are used to report any financial conflicts of interest for the investigators participating in the study.

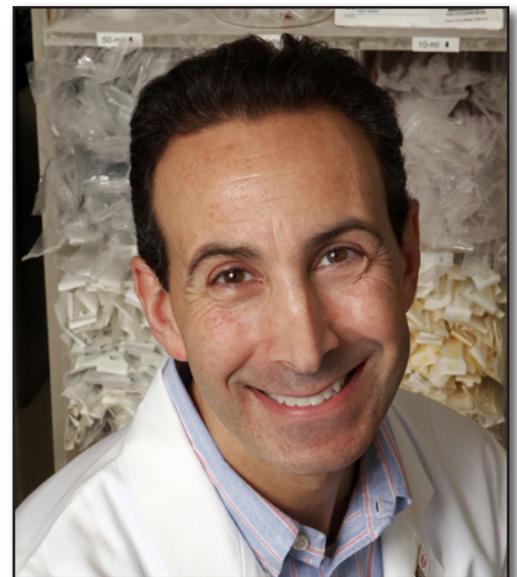
The PTMS allows for electronic submission and approval by the NIH Office of Protocol Services (OPS) at the NIH Clinical Center, which serves as the final reviewing and approving authority for all IRB actions. Approving authorities and PIs sign documents digitally in the system.

Through this web-based system, clinical protocols are centrally stored, highly organized, and available 24 hours a day from any location with internet access. Investigators, study staff, and IRB members can access and review a protocol’s history throughout the life-cycle of the protocol.

PTMS also facilitates IRB meetings, allowing for meetings to be paperless, giving reviewers easy access to protocol information and



*“Before the Protocol Tracking and Management System, IRB administrators were dealing with huge paper files shuffled from desk to desk,” said Pakenham. “With central storage of files, PTMS eliminates the risk of misplacing documents and allows PIs and study staff to access their entire IRB study file.”*  
(Photo courtesy of Steve McCaw)



*“I’m extremely pleased with the job that the OHRC team did in rolling out the new Protocol Tracking and Management System,” said Darryl Zeldin, M.D., acting Clinical Director. “This new system will facilitate the IRB approval process for investigators.”*  
(Photo courtesy of Steve McCaw)

history, and capturing the reviewers' comments. In addition, IRB meeting agendas, minutes, and expedited action reports are generated and stored in the system.

The PTMS system was developed by the National Institute of Neurological Disorders and Stroke (NINDS) for government use. Nine of the twelve NIH Institutional Review Boards use this system for IRB protocol tracking and management. "The PTMS makes the IRB process from submission through approval more efficient," said Pakenham.

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

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*"The new Protocol Tracking and Management System will streamline the IRB process by improving the speed of IRB expedited actions, since it does not require the chair to be on the NIEHS campus to sign documents," said NIEHS Bioethicist and IRB Chair David Resnik, J.D., Ph.D. (Photo courtesy of Steve McCaw)*

## Remembering Superfund Pioneer Dean Carter

*By Eddy Ball*

Binational programs along the U.S.-Mexico border are helping people on both sides live healthier lives because of the efforts of pioneers such as toxicologist Dean Carter, Ph.D., who died May 21 at age 68 in Tucson, Ariz. Carter's initiative and leadership resulted in the establishment in 2003 of the NIEHS-funded [U.S./Mexico Binational Center for Environmental Studies and Toxicology at the University of Arizona \(UA\)](#), which has inspired and served as a model for programs in other border states.

As word spread of Carter's death from complications of Parkinson's disease, friends and colleagues at the university, NIEHS, and elsewhere remembered his monumental contributions to the science and translation of interdisciplinary research.

When he learned of Carter's death, NIEHS Superfund Basic Research Director Bill Suk, Ph.D., spoke of his friend and colleague of more than 20 years. "Thousands of people who will never know how Dean touched their lives are benefiting from his vision and hard work," Suk said.

"Binational programs like the one at UA use health science research to empower and inform people who often live in very difficult conditions to improve the quality of their lives and the lives of future generations," he continued. "Such programs take scientific research out the lab and into the communities where it can make a real difference in health, quality of life, and longevity."



*Describing Carter, above, colleague Glenn Sipes, Ph.D., head of the department of pharmacology in the College of Medicine at UA, said, "He was a gentle man who had a remarkable career that enriched the lives of so many." (Photo courtesy of the University of Arizona Superfund Research Program)*

A native of Michigan, Carter was a faculty member at UA from 1973 until 2007. He built an outstanding career in metals toxicology and established a research program at the UA that was continually funded by federal, state, foundation, and industrial sources. In 1992 he received the prestigious Education Award from the Society of Toxicology for his critical role in developing the toxicology program at UA. Carter also promoted interdisciplinary research and developed a unique outreach program for communities along the Arizona-Mexico border.

During his career at the university, his research resulted in more than 100 peer-reviewed publications, along with 10 books or book chapters. The web-based toxicology textbook that he co-authored, [Toxicologia Ambiental](#), receives more than 50,000 visits per month from Spanish-speaking countries. In 2008, Carter received the Achievement Award from the Metals Specialty Section of the Society of Toxicology in recognition of his career accomplishments.

“More than 20 years later, Dean’s legacy of interdisciplinary research continues,” said [A. Jay Gandolfi, Ph.D.](#), associate dean for research and graduate studies in the College of Pharmacy at UA. “The [University of Arizona Superfund Research Program](#) was renewed until 2015 [by NIEHS] and involves investigators from five colleges. It is truly a model for interdisciplinary research.”

Memorial services were held June 26 at Trinity Presbyterian Church in Tucson. Carter is survived by his wife, sister, daughter, and grandson.

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# Science Notebook

## Non-coding RNAs: What To Be or Not To Be

By Emily Zhou

In a June 3 presentation at NIEHS, guest lecturer John Rinn, Ph.D., explored the role of large non-coding RNAs in establishing the distinct epigenetic states of adult and embryonic cells and their misregulation in cancer. The talk, titled “Large Intergenic Non-coding RNAs (lincRNAs): From Discovery to Mechanism,” made a connection between epigenetic alterations and the environmental factors that trigger their ultimate manifestation. NIEHS Program Administrator Fred Tyson, Ph.D. hosted the [session](#).

A professor in the Department of Pathology at the Harvard Medical School and the Beth Israel Deaconess Medical Center and an associate member of the Broad Institute, [Rinn](#) is an expert in the field of lincRNA, which is a previously unrecognized class of mammalian genes that do not encode proteins, but instead function as long RNA molecules.

Rinn’s research has advanced the understanding of once disregarded non-coding RNAs and revealed that these lincRNAs play critical roles in both health and disease. As a young research investigator recently awarded the Damon Runyon-Rachleff Innovation Fellowship, Rinn already has many peer-reviewed papers published in top scientific journals such as Nature and Science. He has also received an NIH New Innovator Award.

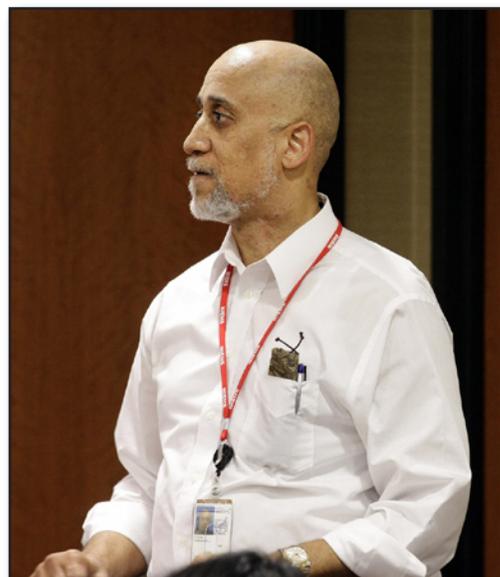
### What to be or not to be

This is the ultimate genomic question, according to Rinn, who opened his seminar by bringing up the fact that “the exact same genome is present in every single cell in our body.” However, he asked, how does the cell decide to either stay in its undifferentiated state or become a heart cell, lung cell, or brain cell? “It is the alternate conformation or epigenetic landscape that it [a cell] takes on that will manifest its different cellular physiologies,” Rinn explained.

Through the efforts of the NIH Roadmap Epigenomics Program led by NIEHS, it is now known that there are different epigenetic markers, such as the histone code, that control cell identity. But how do these bar codes get put there in the first place and how do they maintain control or epigenetic memory in cell division and repair? Rinn contends that lincRNAs are a merging class of transcripts that are able to rearrange the bar codes to guide cell fates.



*“Although I will talk about epigenetics in the bottom state, a lot of it has to do with the signal that was triggered by the damaged cells, which could come from the environment,” said Rinn. “Pathways in the cell respond to the damage that environmental hazard causes to a human cell.” (Photo courtesy of Steve McCaw)*



*During his introduction, Tyson said he’d been intrigued by a recent talk by Rinn and wanted to give his colleagues an opportunity to hear of Rinn’s work in a field the speaker described as “the mysterious world of Noncodarnia.” (Photo courtesy of Steve McCaw)*

## LincRNAs and how to find them

Genes that encode lincRNAs are conserved across mammalian evolution. LincRNAs were considered genomic oddities until recently, when Rinn's laboratory identified large numbers of genes encoding LincRNAs. The researchers surveyed genomic regions that have the same chromatin patterns as protein-coding genes, but do not encode proteins. According to Rinn, roughly 7,000 lincRNAs have been discovered in the human genome so far.

## LincRNA functions

Using lincRNA array, Rinn's group has found evidence that lincRNAs are strongly implicated in embryonic stem cell pluripotency regulation and in cell cycle regulation, especially via the p53 pathway. These lincRNAs are independently regulated and are not correlated with its counterpart coding protein.

Rinn and colleagues have discovered that the lincRNA-regulator of apoptosis in reprogramming (lincRNA-ROAR) is a pro-survival signal that plays an important role in the reprogramming process of fibroblast differentiating into embryonic stem cells to prevent apoptosis. The presence of lincRNA-ROAR increases both the number of induced pluripotency cells (iPSCs) and the size of iPSCs.

LincRNA-p21 is a bona fide p53 transcriptional target that acts as a pro-apoptotic signal. LincRNA-p21 is both necessary and sufficient for triggering apoptosis by mechanistically controlling gene-promoter binding to shut off gene transcription. There are more than 30 lincRNAs in the p53 pathways that await further functional studies.

Rinn's talk was part of the popular Keystone Science Lecture Seminar Series, which is organized and sponsored by the NIEHS Division of Extramural Research and Training.

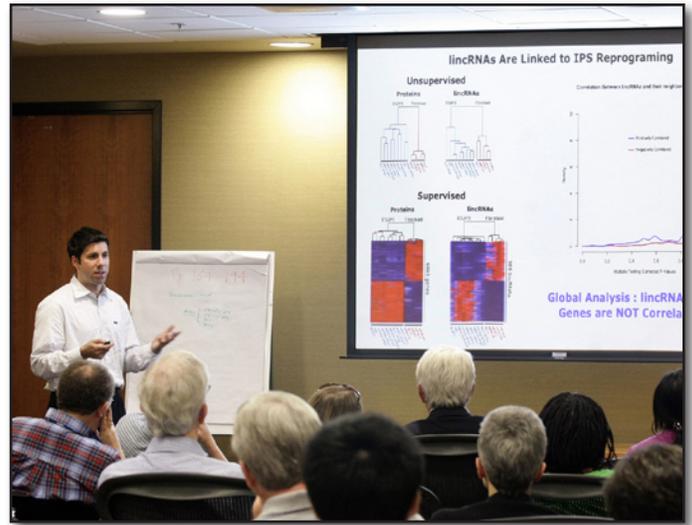
(Yixing [Emily] Zhou, Ph.D., is a postdoctoral research fellow in the NIEHS Laboratory of Signal Transduction.)

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## Arsenic Exposure Shown to Increase Risk of Death

*By Rebecca Wilson*

According to a new [NIEHS-funded](#) study, 35-77 million Bangladeshis may face a higher risk of death from chronic exposure to arsenic in their drinking water. Superfund Research Program researchers at Columbia University, led by [Habibul Ahsan, M.D.](#), published this finding June 19 online in *The Lancet*. They report that in their six-year cohort study nearly 21 percent of deaths from all



*"Now we have a global and generic model in which some transcription factor activates polymerase to make lincRNA, then the lincRNA associates with either repressor or activator and translocates to DNA to allow gene repression or gene activation," Rinn told the audience. (Photo courtesy of Steve McCaw)*



*Lead author Habibul Ahsan (Photo courtesy Habibul Ahsan and CUSRP)*

causes and 24 percent of deaths linked to chronic disease could be attributed in part to drinking arsenic-contaminated water. A unique aspect of their [study](#) is that arsenic exposure has been followed at the level of the individual in nearly 12,000 adults ([see CNN video](#)).

In the prospective “Health Effects of Arsenic Longitudinal Study” (HEALS), trained physicians unaware of the levels of exposure conducted in-person interviews and clinical assessments of 11,746 adults from Araihasar, Bangladesh. Roughly 24 percent of the participants had arsenic concentrations in well water less than 10 micrograms per liter ( $\mu\text{g/L}$ ), the World Health Organization recommended standard, and 45 percent had less than  $50\mu\text{g/L}$ , the Bangladeshi standard. These exposure levels are similar to other populations around the world that have low levels of arsenic in their water.

Following recruitment and baseline assessments, the physicians followed up biennially with participants for six years. During the study period, there were 407 deaths, the causes of which were identified using a validated verbal autopsy questionnaire given to family or neighbors. The findings showed an increased risk of death with increasing concentrations of arsenic in the well water.

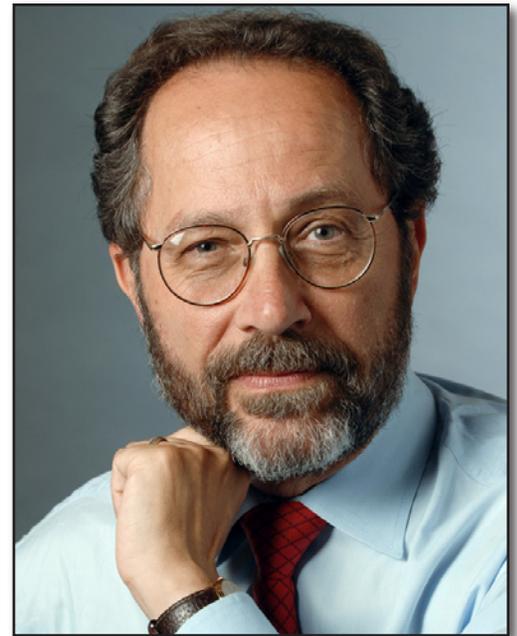
The mortality rate also increased with increasing arsenic consumption over time, regardless of the concentration of arsenic in the well water, “indicating an increasing risk rather than a threshold effect,” the authors wrote. The increased risk seems to persist even after reduction of exposure for up to four years.

The drinking water contamination problem began in Bangladesh in the 1970s, when aid organizations dug millions of hand-pump wells in an effort to provide clean, pathogen-free drinking water to the residents. What they didn’t know at the time is that the water was contaminated with elevated levels of naturally-occurring arsenic ([see BBC story](#)). According to [UNICEF](#), the arsenic wasn’t detected until the early 1990’s. The World Health Organization calls this situation “the largest mass poisoning of a population in history.”

According to Ahsan, it is important to note that the [Columbia University Superfund Research Program \(CUSRP\)](#) has also made great strides in reducing arsenic exposure in their study population. The cohort has recently been expanded to 20,000 for examining rarer health outcomes. Also, one of Ahsan’s newly established projects is to evaluate nutritional interventions to minimize health impacts of arsenic.

In a talk last year at Duke University, CUSRP Director Joseph Graziano, Ph.D., a coauthor on this study, described some of the program’s remediation efforts in the region ([see story](#)).

*Citation:* Argos M, Kalra T, Rathouz PJ, Chen Y, Pierce B, Parvez F, et al. 2010. Arsenic exposure from drinking water, and all-cause and chronic-disease mortalities in Bangladesh (HEALS): a prospective cohort study. *Lancet*. Epub ahead of print. doi:10.1016/S0140-6736(10)60481-3



*Principal Investigator Joseph Graziano  
(Photo courtesy Joseph Graziano and CUSRP)*



*CUSRP team member Karrie Radloff, center in red shirt, works with Bangladeshi residents to sample local wells. Radloff is the 2009 winner of the Wetterhahn Award presented each year by the NIEHS Superfund Basic Research Program to recognize outstanding research contributions by students.. (Photo courtesy of CUSRP)*

(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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## Pollution Linked to Severity of Sleep-Disordered Breathing

By *Negin Martin*

In addition to restless nights and increased daytime sleepiness, sleep-disordered breathing (SDB) is linked to pulmonary, cardiovascular, and autonomic nervous system dysfunction. A new study led by investigators at the Harvard School of Public Health (HSPH) and funded in part by [NIEHS](#) found the first link between air pollution exposure and SDB, a known cause of cardiovascular disorders.

### Collaborative effort among statisticians, physicians, and epidemiologists

The [results](#) were published ahead of print in the American Journal of Respiratory and Critical Care Medicine. The lead author, biostatistician [Antonella Zanobetti, Ph.D.](#), is a senior research scientist in the Department of Environmental Health at the HSPH, who applies her expertise to analyzing epidemiological data linking pollution to morbidity and mortality. Zanobetti's collaborators, second author [Susan Redline, M.D.](#), from the Division of Sleep Medicine at Case Western Reserve University, and Harvard University Professor [Diane Gold, M.D.](#), the principal investigator on the study, are physicians dedicated to uncovering the effects of environment on human health. The group used data from the Sleep Heart Health Study (SHHS) and U.S. Environmental Protection Agency (EPA) air pollution monitoring results to draw conclusions for their research.



*Lead author Zanobetti provided the biostatistical expertise to analyze discrete associations between pollution and SDB. (Photo courtesy of Antonella Zanobetti)*

In a Brigham and Women's Hospital [press release](#) June 14, Zanobetti said of the findings, "We found novel evidence for pollution and temperature effects on sleep-disordered breathing. ... Increases in apnea or hypopnea ... were associated with increases in short-term temperature over all seasons, and with increases in particle pollution levels in the summer months."

### SDB is a silent killer

According to the researchers, abnormalities of breathing pattern during sleep often go unnoticed. SDB affects approximately 17 percent of U.S. adults and the percentage may be higher in poor urban areas, making the condition a significant public health problem.

The most common SDB disorder is the obstructive sleep apnea (OSA), which is total or partial collapse of the pharyngeal airways during sleep. OSA episodes may repeat over the course of the night and are only relieved by sleep arousal or waking up. SDB contributes to hypoxemia — reduced oxygen levels in blood — and respiratory acidosis. Many individuals afflicted with SDB are unaware of their condition and remain undiagnosed.

## The study analyzed data from a large cohort

Over 6000 adults over the age of 39 were recruited for the SHHS cohort study on the health consequences of SDB. The subjects included individuals from major urban cities — Phoenix, Tucson, Sacramento, Framingham, Mass., Minneapolis, New York, and Pittsburgh. The comprehensive study included multiple health readings to determine oxygen levels, brain activity, quality of breathing, movement during sleep, and ambient environment.

Researchers defined an SDB episode as a decrease in chest movement amplitude of less than 75 percent (for apnea) and less than 30 percent (for hypopnea) that lasted at least 10 seconds and resulted in decreased airflow. The frequency of episodes was compared to the air quality data from EPA. Levels of particulate matter with diameter less than 10 micrograms (PM10) – mostly associated with traffic — determined the pollution exposure. Data was analyzed using linear regression models that took into account average temperature and season as well as potential SDB predictors such as age, body mass index, gender, education, smoking, and drinking habits.

## Seasonal and temperature variation affects symptoms

During summer months, short-term changes in levels of PM10 pollution were associated with increased respiratory disturbances and sleep inefficiencies. Elevated PM10 levels also correlated with an increase in the amount of time that volunteers' blood oxygen saturation levels fell below 90 percent. Populations with these types of SDB episodes are more prone to cardiovascular morbidity.

Researchers also discovered that short-term temperature increases were coupled to higher incidence of apnea and hypopnea throughout the year.

Zanobetti and colleagues hypothesized that particulate matter in pollution may increase SDB by influencing the central nervous system and the upper airways. Air pollutants also contain allergens that could induce inflammation and trigger an allergic response contributing to SDB.

The study lends strength to the argument that reduction in pollution exposure may lower cardiovascular risk by reducing the frequency and severity of SDB.

*Citation:* [Zanobetti A, Redline S, Schwartz J, Rosen D, Patel S, O'Connor GT, et al.](#) 2010. Associations of PM10 with Sleep and Sleep-disordered Breathing in Adults from Seven U.S. Urban Areas. *Am J Respir Crit Care Med*. Epub ahead of print. doi:10.1164/rccm.200912-1797OC



*Gold is the principal investigator on the study and on the NIEHS grant that contributed support to the investigators. Including this latest study, there are now 59 publications associated with the grant, “Ambient Particles and Cardiac Vulnerability in Humans,” which has been administered by Program Administrator Kimberley Gray, Ph.D., and Health Science Administrator Caroline Dilworth, Ph.D., (Photo courtesy of Diane Gold)*



*Second author Redline is a nationally recognized authority in the effects of sleep disorders on health who was referenced in a June 18 Newsweek article, “The Surprising Toll of Sleep Deprivation.” (Photo courtesy of Susan Redline)*

(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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## Identifying Environmental Carcinogens Through Epidemiology

By Jeffrey Stumpf

During his visit to NIEHS June 17, guest lecturer Paolo Boffetta, M.D., deputy director of the Tisch Cancer Institute at the Mount Sinai School of Medicine, explored the topic of “Environmental Cancer Epidemiology: Challenges and Perspectives.” Hosted by NIEHS/NTP Director Linda Birnbaum, Ph.D., Boffetta’s talk focused on the identification of environmental risk factors that lead to cancer, a challenge that is central to the mission of NIEHS.

As Boffetta explained, a growing and aging world population with increasing exposures to environmental risk factors is projected to experience more than twice the number of cancer deaths in the next thirty years. Known risk factors include tobacco, alcohol, chronic infections, poor nutrition, hormonal changes, ionizing and solar radiation, and occupational and environmental factors such as radon decay, tobacco smoke, smoke from burning coal, asbestos, and arsenic in water.

Boffetta referred to a 2000 study in France showing that known carcinogenic risk factors, although important, explain only one-third to one-half of the incidences of cancer. According to Boffetta, carefully designed epidemiological studies can be useful in filling this knowledge gap by identifying novel environmental carcinogens that could explain some of the remaining cancer incidences.

### Challenges of cancer epidemiology

Boffetta outlined several disadvantages of epidemiology studies of cancer. He said data is pooled from several studies to obtain large enough data sets needed to identify small effects. Unfortunately, such meta-studies are subject to several biases, including information bias. Also, study design and data collection may vary among different studies.

To illustrate the difficulties of cancer epidemiology, Boffetta pointed to studies of three suspected carcinogens — water-chlorinated by-products, pesticides, and outdoor air pollution. The pooling of data from six independent studies suggests a small correlation between water-chlorinated by-products and bladder cancer. Although early studies in pesticides were promising, the correlation between dichlorodiphenyldichloroethylene (DDE), a breakdown product of the banned pesticide [dichlorodiphenyltrichloroethane \(DDT\)](#), and breast cancer decreased in more recent studies, possibly due to more limited exposure. Although several researchers have proposed that fine particle outdoor air pollution may pose a potential lung cancer risk, Boffetta said that the available data do not support a definite conclusion.



*Boffetta, above, has held several academic posts and is currently an adjunct professor in the Department of Epidemiology at the Harvard University School of Public Health. Prior to joining the Tisch Cancer Institute, he served as the head of the Gene-Environment Epidemiology Group at the International Agency for Research on Cancer, a unit of the World Health Organization. (Photo courtesy of Paolo Boffetta)*

Duration studies of lung cancer risk due to second-hand smoke have explored the association between increased lung cancer risk and number of years of exposure, but Boffetta said he found only “very weak evidence” in support of this hypothesis. One possible reason, he speculated, could be that people in the study were misclassified as smokers or nonsmokers. Also, the duration of exposure was inaccurate in some cases because the people in the study may not have quit smoking when they reported.

### **Solution lies in larger studies**

In response to the challenges of environmental cancer epidemiology, Boffetta outlined the feasibility study for his newest project. The study will be conducted using a cohort of an estimated 300,000 middle-aged people in Daqing, China, a city whose workforce is primarily involved in oil production.

The goal of the study is to make periodic exposure assessments through biological samples while tracking lifestyle habits and medical conditions. High-risk individuals will be selected for early diagnosis and intervention. Boffetta said he is hopeful that the duration of the study will help in identifying potential carcinogens over an extended period of time. “We plan to be collecting data in three years,” he explained, “but the study will hopefully go on for years to come.”

Boffetta acknowledged that a large-scale study also has its potential pitfalls. The power of such a study depends to a great extent on the frequency of measuring environmental exposures. If performed infrequently, researchers will not be able to detect acute exposures. As Boffetta observed in response to a question from the audience, epidemiology studies will not determine risk factors in all cancers. Still, he believes that large-scale studies will provide greater support for the characterization of environmental exposures as carcinogens and better identify novel cancer risks.

(Jeffrey Stumpf, Ph.D., is a postdoctoral fellow in the NIEHS Laboratory of Molecular Genetics Mitochondrial DNA Replication Group.)

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## **Discovery May Open Doors for New Blood Pressure Treatments**

*By Robin Mackar*

NIEHS-funded researchers have found that increasing certain proteins in the blood vessels of mice relaxed the vessels, lowering the animal’s blood pressure. Their study, published online in *The FASEB Journal*, provides new avenues for research that may lead to new treatments for hypertension.

“The paper demonstrates that cytochrome P450 plays an important role in the management of high blood pressure, a disease of enormous public health concern,” said [Darryl Zeldin, M.D.](#), acting clinical director of the National Institute of Environmental Health Sciences (NIEHS) and senior author on the paper.

### **Audience Response**

Boffetta’s talk attracted an audience from throughout the Institute, including NIEHS Senior Advisor [Chris Portier, Ph.D.](#), who is part of the Institute’s global health initiative. Portier was the NIEHS lead on a series of studies published in November 2009 in the medical journal *The Lancet* on the potential impact of climate change on household energy, transportation, electricity generation and agricultural food production. ([see story](#))

Asked about his impression of the seminar, Portier said he agrees with Boffetta that believe epidemiological studies can contribute significantly to identifying and quantifying risks from exposure to toxic chemicals. However, these studies still pose challenges. “The difficulty,” Portier observed, “is in understanding how these data, in concert with the toxicological evidence, provide evidence of serious human harm.”

According to the Centers for Disease Control and Prevention, about 1 in 3 adults in the United States has **high blood pressure**, which increases the risk for heart disease and stroke, the first and third leading causes of death in the United States.

The **study** was conducted by researchers at NIEHS who teamed with investigators at the University of North Carolina at Chapel Hill (UNC), Medical College of Wisconsin, Milwaukee, and Oregon Health and Science University, Portland.

The researchers created animal models that had a human cytochrome P450 (CYP450 or P450) in the cells that line their blood vessels. The mice with the P450 generated more substances called epoxyeicosatrienoic acids or EETs, which are known for their role in protecting the cardiovascular system. EETs relax and dilate the blood vessels and fight inflammation.

“We found that when the animals were exposed to substances known to increase blood pressure, the animals with the P450 had lower blood pressure and less damage to the kidneys compared to normal mice,” said **Craig R. Lee, Pharm.D., Ph.D.**, assistant professor at the University of North Carolina at Chapel Hill (UNC-CH) and lead author on the paper. “We hope that these studies will advance the development of new treatments for high blood pressure.”

“This is a great example of a basic finding that improves our understanding of a metabolic pathway that can be used to develop improved treatments for those suffering from a common disease like hypertension,” said Linda Birnbaum, Ph.D., director of NIEHS and the National Toxicology Program.

“The research collaboration also provides an excellent real life example of how we are mentoring and supporting young investigators at NIEHS for their own research careers,” Birnbaum added. Lee was a trainee with Zeldin’s Environmental Cardiopulmonary Disease Group in the NIEHS Laboratory of Respiratory Biology (see text box).



*Lee, above, said of his experience in Zeldin’s group, “I will always be grateful for the tremendous mentorship of Dr. Zeldin and support from NIEHS.” (Photo courtesy of Craig Lee)*



*Principal Investigator Darryl Zeldin led the 18-member research team that also included scientists from the NIEHS Laboratory of Structural Biology. (Photo courtesy of Steve McCaw)*

## **NIEHS Training Experience Shapes Research**

Lee completed his dissertation research at NIEHS in the Laboratory of Respiratory Biology under the mentorship of Zeldin. Lee is now an assistant professor at UNC-CH Eshelman School of Pharmacy and the recent recipient of an NIH grant to continue his work in this area. In 2007, he received a **beginning grant-in-aid** from the American Heart Association.

“Development of this mouse model was an integral part of my training at NIEHS,” Lee said. “It will enable investigators to better understand the role of the P450-EET pathway in various diseases that are impacted by blood vessel function, and is a key component of the ongoing collaboration between my lab at UNC and NIEHS.”

*Citation:* Lee CR, Imig JD, Edin ML, Foley J, DeGraff LM, Bradbury JA, et al. 2010. Endothelial expression of human cytochrome P450 epoxygenases lowers blood pressure and attenuates hypertension-induced renal injury in mice. FASEB J. Epub ahead of print. doi:10.1096/fj.10-160119.

(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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## Mutations – Raw Materials for Bacterial Evolution

*By Sophie Bolick*

Ivan Matic, Ph.D., a leading molecular geneticist with the French National Institute of Health and Medical Research in Paris, visited NIEHS June 7, as a guest of the Laboratory of Molecular Genetics (LMG) fellows. Matic spoke on the “Modulation of Mutation Rates in Bacteria,” exploring the mechanisms of genetic alterations that play a key role in human disease causation and drive evolution.

The lecture was hosted by Postdoctoral Fellow Richard Gradman, Ph.D., a member of the LMG Spontaneous Mutation and DNA Repair Group.

### Role of mutations in biological evolution

“Genetic viability is the basis for most evolutionary processes and is primarily produced by mutations,” began [Matic](#). Newly arising mutations are essentially neutral or deleterious and occur at higher rates than lethal or adaptive mutations. However, what is deleterious in a given environment can be adaptive in another environment.

There is a significant physiological cost attributed to the maintenance of the low mutation rates, due to the large number of proteins involved. There are numerous proteins that contribute to DNA replication fidelity in *Escherichia coli* (*E. coli*). DNA mismatch repair (MMR), which controls DNA replication fidelity, is one of the main DNA repair mechanisms a cell has to recognize and eliminate mismatched or unpaired bases in replicated DNA.

For this to occur, MMR differentiates between the DNA template strand, which is methylated, and the newly synthesized DNA strand, which is not. This process corrects 99 percent of replication errors in *E. coli*. As Matic demonstrated in a series of experiments ([see text box](#)), several proteins are involved in this process: MutS, which binds mismatched bases; MutL, which recruits MutH to the complex; and MutH, which cleaves the DNA.



*Speaking to many familiar faces, Matic said of his research, “If we want to look at selective pressures, we have to go back to nature or bring nature back to the lab.” (Photo courtesy of Steve McCaw)*

## Selective pressures and evolution

Optimizing selection takes into account a statistically continuous distribution. Individuals who have extreme values of trait have lower fitness than individuals in the middle of distribution.

To study this, Matic took 70 *E. coli* natural isolates and placed them under identical experimental conditions and measured their capacity to generate mutations. He found that mutation rates are not low and are highly variable. Nearly all strong mutators were MMR deficient mutants. “There must be strong selective pressure under certain conditions that favors mutation,” reasoned Matic, because, according to theory, if an organism produces 100-fold more advantageous mutations, it is also producing 100-fold more deleterious and lethal mutations, so some of these strains should be dead, but they are not.



*Waiting to ask a question, Dmitry Gordenin, Ph.D., staff scientist with the LMG Chromosome Stability Group, center; listened attentively. Also pictured are lecture host Richard Gradman, left, and Anders Clausen, Ph.D., postdoctoral fellow in the DNA Replication Fidelity Group. (Photo courtesy of Steve McCaw)*

## Experimental evolution in mice

The studies with the bacterial isolates were extended to germ-free mice colonized with the same bacterial strains and then continuously exposed to a series of antibiotics. Samples were taken every day, explained Matic, “So you can freeze evolution and go back and ask what’s happening.” Over time, the mutation rates increased. At the end of the experiment, there were 100 percent mutators.

Mutator populations are generating mutations to these antibiotics at high rates. What is happening in mice? “Mutators need smaller population size in order to generate new adaptive mutations than non-mutators. Hence, when selective pressure is very strong, you need multiple mutations in a small period of time in the same genome. A non-mutator cannot do this because he has no time.”

## Most mutator strains are mismatch repair deficient mutants

“Why is this?” asked Matic. “We don’t necessarily have the answer, but I have a few ideas,” he added. “First, MMR is not a DNA repair system, at least in bacteria. The mismatch repair system is eliminating replication errors. There is a reason you don’t find DNA repair mutants that are mutators in the laboratory or in nature. If you’re not repairing DNA lesions, you’re dead. It’s very dangerous. That’s why you have all these natural MMR mutants.”

“The second thing is MMR is not only controlling replication fidelity but also the fidelity of homologous recombination efficiency. MMR deficient alleles can hitchhike with mutations and recombination events,” he continued. “One recombination event is less deleterious than one newly arising mutation, simply because with recombination you’re reshuffling mutations that have already undergone natural selection.”

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

## An Experimental Approach For Detecting Mutations

Matic fused green fluorescent protein (GFP) to the proteins MutL and MutS, respectively, and used them to detect mismatches in bacterial cells as visualized by fluorescent foci. These studies showed that there is 2- to 10-fold more MutL in cells than MutS per mismatch in the absence of MutH. Matic thinks that communication between mismatches and strand-discrimination site, the MutH cutting site, is achieved by multimers — proteins made up of more than one peptide chain — of MutL. These constructs are currently used as tools for studying molecular mechanisms of mismatch repair in his lab.

The next question Matic asked was “What is happening with the foci?” He found that any given foci disappeared within 40 minutes, which is the replication time for *E. coli*. The disappearance of foci indicates that the mutation was fixed at that moment. Additional experiments showed that the number of MutL-GFP foci was linearly related to the frequency of mutations.

“What you have here is the possibility for visualization of replication errors in live organisms,” said Matic. “What’s even more amazing is that method is allowing you to score most emerging mutations independently of their phenotype.”

However, as Matic discovered, there are limitations to this assay. Certain mismatched bases, like a C-C mismatch, cannot be detected. If the clusters of mutations are too close, they are not distinguishable.

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## Little Things That Do a Lot

By Emily Zhou

The July 7 presentation in the Laboratory of Signal Transduction (LST) Seminar Series featured Les Hanakahi, Ph.D., from the Department of Medicinal Chemistry and Pharmacognosy at the University of Illinois College of Pharmacy at Rockford. Her talk, “Little Things that Do a Lot: Inositol Polyphosphates in DNA Repair,” was one of the highlights of the Laboratory’s 2010 seminar program.

According to [Hanakahi](#), inositol polyphosphates are important molecules that are crucial in a vast array of cellular physiologies including DNA repair. In a healthy organism, deficits in DNA repair promote development of cancers triggered by accumulated environmental exposures. Conversely, a targeted reduction of DNA repair efficiency in cancer cells by using analogs of inositol hexakisphosphate (IP6) may offer clinicians a novel way to augment traditional therapies.

Hanakahi’s research on the role of inositol polyphosphates in DNA repair has advanced the understanding of how a molecule such as IP6, while small, can nevertheless have a considerable role in regulating some of the multi-protein interaction that are so critical to the complex process of DNA repair.



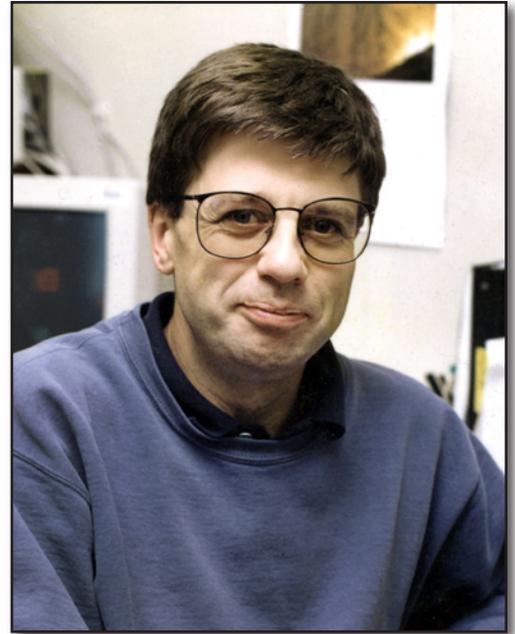
*Hanakahi, above, said she is excited by the possibility that synthetic or natural products resembling IP6 may be used to control the efficiency of NHEJ in human cells, opening up possibilities in the understanding and treatment of cancer. (Photo courtesy of Les Hanakahi)*

## Double-stranded DNA repair

Over 95 percent of cells in human body reside in the G1 (gap 1)/G0 (resting) phase of the cell cycle. Upon ionizing radiation (IR) exposure or other environmental intrusion, double-stranded DNA break (DSB) occurs. Non-homologous end joining (NHEJ) is the process that is responsible for repairing DSB in G0 and G1 phases of the [cell cycle](#).

“Consequences of DSB repair failure are gross chromosomal aberrations that may lead to cancer,” said Hanakahi. NHEJ involves multi-protein complexes such as Ku70/80, DNA-protein kinase (DNA-PK), X-ray repair complementing defective repair in Chinese hamster cells 4 (XRCC4), Ligase IV, and XRCC4-like factor (XLF). The presence of IP6 significantly stimulates NHEJ *in vitro* in a time dependent manner. Furthermore, it is the specific binding of IP6 to Ku70/80 complex, not other components of NHEJ, that results in the stimulation of NHEJ.

Mutants of Ku70/80 that cannot bind IP6 fail to stimulate NHEJ. Future studies that involve knock-down of Ku70/80 in rodent cell lines and knock-in mutants of Ku70/80 in human cells are being carried out to more clearly define the role of IP6 in NHEJ. The potential role in NHEJ of diphosphorylated derivatives of IP6, such as IP7 or IP8, is also under investigation in Hanakahi’s laboratory.



*Shears commented that Hanakahi “received more incisive questions regarding inositol phosphates than I do [after a presentation],” even though her background is the DNA repair field. (Photo courtesy of Steve McCaw)*

## Human adenovirus infection and NHEJ

Scientists frequently explore the details of cellular physiology through the interaction between a pathogen and its host. “By using human adenovirus as a tool to study mammalian NHEJ,” Hanakahi explains, “we have uncovered a novel aspect of NHEJ — in human cells, DNA recognition by XRCC4 and XLF requires the ligase IV polypeptide.”

Experiments from Hanakahi’s laboratory have also shown that infection of human cells with human adenovirus type 5 causes inhibition of NHEJ both *in vitro* and *in vivo*, loss of DNA ligase IV, and loss of DNA binding by XRCC4 and XLF. Hanakahi hypothesizes that intrinsic DNA binding activities by XRCC4 and XLF are regulated through phosphorylation. Further experiments are underway to identify these putative kinases. Whether this phosphorylation involves the Ku70/80-IP6 complex is being explored.

## Therapeutic possibilities

“The discovery that IP6 stimulates mammalian NHEJ *in vitro* suggests the exciting possibility that synthetic or natural products resembling IP6 may be used to control the efficiency of NHEJ in human cells,” said Hanakahi. “An example of the utility of such IP6-analogs is reduction of NHEJ efficiency in tumor cells, which could augment traditional radiation therapy by preventing DSB repair in cancer cells. This would decrease tumor cell viability and promote reductions in tumor mass.”

As seminar host LST Principal Investigator Stephen Shears, Ph.D., observed afterwards, Hanakahi engaged her audience’s interest because of her high quality science, infectious enthusiasm for scientific research, and engaging presentation skills.

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

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# Fire Retardant Chemicals Linked to Lower TSH in Pregnancy

By Tara Ann Cartwright

According to a new study by [NIEHS-funded](#) researchers at the University of California, Berkeley (UCB) exposure to fire retardant chemicals is associated with lower levels of thyroid-stimulating hormone (TSH) during pregnancy.

UCB researcher [Jonathan Chevrier, Ph.D.](#), was first author on the [study](#), which was published online this month in Environmental Health Perspectives. The principal investigator on the study was epidemiologist [Brenda Eskenazi, Ph.D.](#), director of the Center for Children’s Environmental Health Research at the UCB School of Public Health, who presented a distinguished lecture March 16 at NIEHS on her work with farm workers in California exposed to pesticides ([see story](#)).

Eskenazi said of the new study, “Maternal thyroid hormones have been shown to cross the placenta and are essential for normal fetal growth and neurodevelopment, so our findings may have significant public health implications.”

## Discontinued chemicals persist in the environment

Polybrominated diphenylethers (PBDEs) are organobromine compounds, which have been used as fire retardants since the 1970s. Like other brominated flame retardants, PBDEs are a component in a wide array of consumer products such as electronics, toys, clothing, appliances, draperies, carpets, upholstery, and furniture foam.

The commercial mixtures penta-BDE and octa-BDE have been banned in Europe and several U.S. states because of health and safety concerns. The major North American manufacturer of these two PBDEs ceased production in 2004. However, PBDEs are still present in furniture and foam items manufactured before the ban and thus exposure is believed to be ongoing.

Since PBDEs are not chemically bound to the materials in which they are used, they are believed to be slowly and continuously released into the environment over time. Once released into the air, PBDEs can settle on soil or at the bottom of rivers and lakes. According to the authors, exposure to PBDEs is believed to occur primarily indoors, possibly through contact with house dust.

## Health effects could be significant

Although the use of flame retardants is intended to reduce the risk of fire, as well as save lives and property, the potential health hazards of these synthetic chemicals have attracted increased scrutiny. According to Chevrier, in Europe, Asia, North America, and the Arctic, traces of several PBDEs have been found in human



First author Jonathan Chevrier (Photo courtesy of Jonathan Chevrier)



Principal investigator Brenda Eskenazi (Photo courtesy of Brenda Eskenazi)

breast milk, adipose tissue, and serum, and even in wildlife. Over the past three decades, the levels of PBDEs in human breast milk and serum have increased exponentially, and some experts believe they have not yet seen the highest levels.

The study's researchers said that evidence that PBDEs may affect human health is mounting. Animal studies have suggested that exposure to PBDEs impairs neurodevelopment, increases spontaneous motor behavior, and disrupts thyroid hormone (TH) homeostasis. Thyroid hormones are essential for normal fetal neurodevelopment, and human studies suggest that altered neurodevelopment may result from PBDE exposure during critical windows of development.

Taken together, this latest study allows officials from other U.S. states to evaluate the potential adverse health effects of human exposure to PBDEs and, perhaps, will help influence their support for legislative policies and programs to limit exposure to these global contaminants.

*Citation:* [Chevrier J, Harley KG, Bradman A, Gharbi M, Sjödin A, Eskenazi B.](#) 2010. Polybrominated diphenylether (PBDE) flame retardants and thyroid hormone during pregnancy. *Environ Health Perspect*. Epub before print. doi:10.1289/ehp.1001905.

[Herbstman JB, Sjödin A, Kurzon M, Lederman SA, Jones RS, Rauh V, et al.](#) 2010. Prenatal exposure to PBDEs and neurodevelopment. *Environ Health Perspect* 118(5):712-719.

[Roze E, Meijer L, Bakker A, Van Braeckel KN, Sauer PJ, Bos AF.](#) 2009. Prenatal exposure to organohalogens, including brominated flame retardants, influences motor, cognitive, and behavioral performance at school age. *Environ Health Perspect* 117(12):1953-1958.

(Tara Ann Cartwright, Ph.D., is a postdoctoral fellow in the NIEHS Laboratory of Neurobiology Membrane Signaling Group.)

## Large Study Lends Power to Associations

The study is the largest yet to examine the relation between serum PBDE concentrations and thyroid function in pregnant women around the 26th week of gestation. Researchers measured the concentration of PBDEs, free thyroxine (T4), total T4, and thyroid-stimulating hormone (TSH) in serum samples collected from 270 pregnant low-income Latina women living in rural California. All participants were enrolled in a birth cohort study at the [Center for the Health Assessment of Mothers and Children \(CHAMACOS\)](#), a birth cohort study that examines reproductive health and environmental exposures.

Researchers found an inverse association between the serum levels of the PBDE congeners BDE-28, 47, 99, 100 and 153 and thyroid-stimulating hormone (TSH). The odds of developing subclinical hyperthyroidism, defined as TSH below the normal range but normal T4, was also elevated in connection with increasing exposure to total PBDEs and BDE-100 and 153. The researchers detected PBDEs in all women.

“The impacts of hyperthyroidism in pregnancy may be profound as it has been associated with increased risks of miscarriage, premature birth, and intra-uterine growth retardation,” the authors explained. The researchers added a caveat, “It is, however, important to note that the effects of maternal subclinical hyperthyroidism on fetal health are unclear and that more studies are needed on the subject in order to fully understand the implications of our findings.”

# Respiratory Syncytial Virus – Not Just a Children’s Disease

By Laura Hall

“We used to think that respiratory syncytial virus (RSV) is a cause of runny nose and occurs mainly in children,” said NIEHS grantee Sadis Matalon, Ph.D., during his May 25 guest lecture at NIEHS. “It has become very clear recently that RSV is very much undiagnosed and accounts for a large part of the adult pneumonias of unknown cause.”

Matalon discussed the basic mechanisms and physiological consequences of RSV. In his seminar titled “Respiratory Syncytial Virus: From Runny Noses to Pulmonary Edema,” he also talked about his research on RSV and oxidant gas exposure interactions, part of his contributions to the NIH CounterAct Program (see text box).

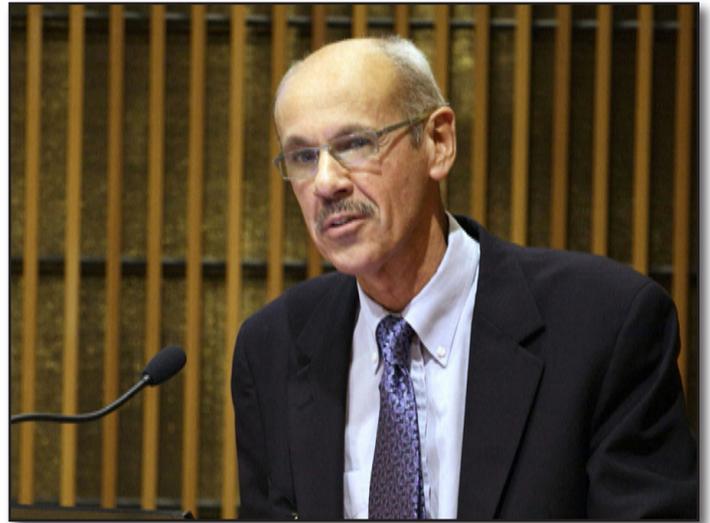
Matalon is the Alice McNeal professor and vice chairman for Research in the Department of Anesthesiology and director of the Pulmonary Injury and Repair Center in the School of Medicine at University of Alabama at Birmingham (UAB).

According to Matalon, RSV can cause serious illness, creating a significant burden on the healthcare system. “RSV is the most common reason that children become hospitalized,” Matalon said. Since the body does not develop permanent resistance to RSV, repeated infections occur and adults are not immune. “There are approximately 170,000 hospitalizations and 10,000 deaths associated with RSV annually in people over 65 years of age in the U.S. alone,” he continued.

## Alveolar ion transport

Matalon described how RSV infection in mice decreases the ion transport across the epithelial cells lining the lungs. These cells, called alveolar cells, line the alveoli — the tiny air sacs of the lung where the exchange of oxygen and carbon dioxide take place.

The alveolar cells separate the air compartment inside the lung and the interstitial space next to the pulmonary blood vessels. A thin layer of liquid is required on the apical, the air-facing side of the alveolar epithelium, in order to permit efficient lung and blood gas exchange. Too much liquid prevents adequate gas exchange and not enough oxygen gets to the cells causing hypoxia. Pulmonary edema occurs when there is too much fluid in the lungs.



*“Every child will get RSV,” Matalon said. “Two to three percent of these cases will require hospitalization.” RSV is also “as deadly as it can come if you are immuno-compromised, irrespective of age,” he added. (Photo courtesy of Steve McCaw)*



*Susceptibility and Population Health Branch Program Administrator Elizabeth Maull, Ph.D., introduced NIEHS grantee Matalon. She mentioned that he has received many honors including a Fulbright Scholarship while attending Macalester College and, just this year, an honorary Doctor of Science from the University of Thessaly in Greece. (Photo courtesy of Steve McCaw)*

Normally, fluid is reabsorbed from the air space into the interstitial space across the alveolar cell to prevent fluid build-up — a process called alveolar fluid clearance (AFC). Sodium and chloride ions pass through ion channels located on the apical alveolar epithelium and water passively follows. The epithelial sodium channels (ENaC) are responsible for this apical sodium movement. On the blood side of the alveolar cell, the sodium-potassium adenosine triphosphate dependent pump (Na,K-ATPase), an ion transporter, pumps sodium out of the cell into the interstitial space.

### RSV mechanism decreasing AFC

Matalon's studies showed that RSV infection decreased AFC by downregulating ENaC, reducing sodium reabsorption into the alveolar cells. The main pathway by which RSV induces ENaC downregulation involves increasing uridine triphosphate (UTP), a signaling molecule. Increased UTP is released from the cells through volume-regulated anion channels and acts on purinergic receptor P2Y. The P2Y receptors then activate an enzyme, protein kinase C zeta, that increases calcium levels, which in turn downregulate ENaC.

Understanding these mechanisms, Matalon explained, may lead to the discovery of interventions that can be effective in treating patients who develop RSV through general environmental exposures or as a result of industrial accidents, natural disasters, or terrorist attacks.

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



*From his work on RSV and chlorine exposure interactions, Matalon knows that some people will be more susceptible to lung damage from chlorine exposure. "Although normal people may not be bothered by a small amount of chlorine or bleach, those people with asthma or infected with RSV could be vulnerable to lung damage if they have to face exposure to chlorine or another oxidant gas," he said. (Photo courtesy of Steve McCaw)*

## Translating Basic Research on RSV to Treatment with CounterAct Funding

In his work for the [UAB CounterAct Research Center of Excellence](#) (see related story), Matalon has investigated chlorine exposure induced lung damage in mice. He has studied the interactive effect of RSV and chlorine exposure to better develop countermeasures against chlorine exposure for people with normal and pre-existing lung conditions.

Matalon's studies showed that mice that were infected with RSV and exposed to chlorine gas developed reactive airway disease syndrome — a disease restricting airflow similar to a persistent asthma syndrome in people who have experienced high irritant exposure. RSV infection alone did not cause the disease, but did sensitize the airways and helped predispose the animals to the development of reactive airway disease after a subsequent exposure to chlorine.

The studies demonstrated that giving exposed animals a long-acting beta2-adrenergic receptor agonist — a drug that opens airways — 10 minutes after exposure could reduce disease symptoms and that repeated doses could prevent symptoms for at least six days.



*Michael Fessler, M.D., NIEHS principal investigator of the Host Defense Group in the Laboratory of Respiratory Biology and of the Environmental Innate Immunity Group of the Clinical Research Program listened carefully to one of the questions at the end of the seminar. He studies lung inflammation and host defense in mouse models and the role of innate immunity in inflammatory lung disease in humans. (Photo courtesy of Steve McCaw)*

# 30 Year Old Research Still Resonates

By Laura Hall

The NIEHS has played a key role in the federal government's response to the massive April 20 Deepwater Horizon oil spill. The NIEHS effort drew upon 24 years of experience providing safety training to emergency responders and hazardous materials workers through the NIEHS [Worker Education and Training Program](#) (See related story). The NIEHS will also fund research on the health effects of the oil spill, which reminded one of NIEHS scientists of some related work he had done decades ago.

Early in his career before joining NIEHS, [David Miller, Ph.D.](#), now chief of the NIEHS Laboratory of Toxicology and Pharmacology, studied the physiological effects of Louisiana crude oil ingestion on seabirds. This research, which was done in the late 1970s and early 1980s, was partially funded by NIEHS and the Canadian Wildlife Service.

The studies reported what happened to several species of seabirds after ingestion of a single small dose — 0.2 to 1.0 milliliter — of crude oil. Birds that ingested oil showed marked reductions in weight and other sub-lethal toxic effects that could have reduced their ability to survive long-term. The birds tested included nestling herring gulls (*Larus argentatus*), nestling black guillemots (*Cephus grylle*), and Leach's Storm-petrels (*Oceanodroma leucorhoa*). Miller conducted the research both in the laboratory and in the field, on islands where the birds nested.

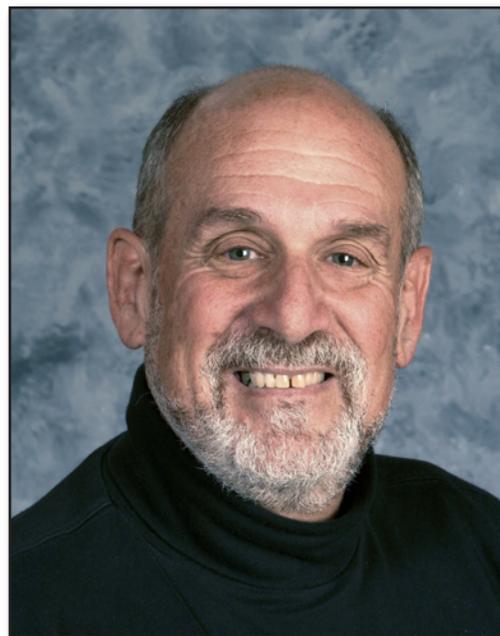
## Endocrine and functional disruption

The data suggested that endocrine disruption was one underlying cause of the reduced growth in young birds. The oil-dosed birds also displayed salt and water balance or osmoregulatory impairment, as well as hypertrophy — abnormal enlargement of the constituent cells — of adrenal and nasal salt glands. Oil dosing reduced nutrient absorption in the intestine and hypertrophy of the liver.

In addition, adult petrels dosed with Prudhoe Bay crude oil were impaired in their ability to provide food for their chicks. Petrel chicks of oil-dosed adults had reduced survival as well as reduced growth rates.

## Insight into the effects of dispersants

Miller's team also compared the effects of Corexit, an oil dispersant, an oil/Corexit emulsion, and oil exposure alone in herring gull nestlings.



*"Seabirds can ingest oil by preening, drinking sea water, or eating contaminated food," said Miller. "The scary part about the results is that only one small dose is likely to give the birds problems with long-term survival." He added, "Nestling herring gulls experienced a 40 to 80 percent reduction in weight gain after one dose of crude oil." (Photo courtesy of Steve McCaw)*



*Heavily oiled Brown Pelicans captured at Grand Isle, La. on June 3, wait to be cleaned of Gulf spill crude at The Fort Jackson Wildlife Care Center in Buras, La. In Miller's experiments, only small sections of the birds were covered with four grams of oil or emulsion — just enough to see if there was an effect. (Photo courtesy of Jay Holcombe and the International Bird Rescue Research Center)*

Ingested dispersant had no effect on weight and the effects of emulsion were no different from those of oil. However, when emulsion was applied externally on the birds, body weight declined and thyroid hormone levels increased. No such changes were seen when oil alone was applied externally. The scientists suggested that external emulsion primarily altered the birds' energy metabolism, probably to compensate for heat loss.

Weight loss in nestlings that continues after fledging can decrease long-term survival in ocean birds. Not only must these young birds find their own food, but after fledging many undertake long migrations or travel far into the ocean. Lowered body weight puts them at a competitive disadvantage.

### **Persistent toxicity**

Normally, crude oil rapidly weathers after a spill, losing the more volatile and water soluble components within a few hours. However, Miller and his colleagues found that the weathering of South Louisiana crude oil did not alter its toxicity and that the higher molecular weight aromatic compounds — polynuclear aromatics with three or more ring structures — were responsible for toxicity in the birds.

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

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## **Effects of Crude Oil Ingestion on Seabirds**

Miller's studies of seabirds were published between 1978 and 1985. Citations to articles available on line or abstracted by the National Library of Medicine contain links. Studies that were not abstracted or, in some cases, not even indexed by PubMed may be available through inter-library loan or in some library collections.

*Citations:*

[Miller DS, Kinter WB, Peakall DB](#). 1978. Ingestion of crude oil: Sublethal effects in herring gull chicks. *Science* 199:315-317.

[Peakall DB, Miller DS, Kinter WB](#). 1979. Physiological Techniques for assessing the impact of oil on seabirds. In: *Avian and Mammalian Wildlife Toxicology* (Kenaga EE, ed.). Philadelphia, Pa: American Society for Testing and Materials, 52-60.

[Peakall DB, Miller DS, Butler RG, Kinter WB, Hallett, D](#). 1980. Sublethal effects of crude oil on Black Guillemots: A combined field and laboratory study. *Ambio* 9:28-30.

[Peakall DB, Tremblay J, Kinter WB, Miller DS](#). 1981. Endocrine dysfunction in seabirds caused by ingested oil. *Environ Res* 24:6-14.

[Miller DS, Hallett DJ, Peakall DB](#). 1982. Which components of crude oil are toxic to young seabirds? *Environ Toxicol Chem*. 1:39-44.

[Peakall DB, Kinter WB, Miller DS](#). 1983. Toxicity of crude oils and their fractions to nestling herring gulls 1. Physiological and biochemical effects. *Marine Env Res* 8:63-71.

[Trivelpiece W, Butler RG, Miller DS, Peakall DB](#). 1984. Reduced survival of chicks of oil-dosed adult Leach's Storm-Petrels. *Condor* 86:81-82.

[Peakall DB, Jeffrey DA, Miller DS](#). 1985. Weight loss of herring gulls exposed to oil and oil emulsion. *Ambio* 14:108-110.

[Jeffrey DA, Peakall DB, Miller DS, Herzberg GR](#). 1985. Blood chemistry changes in food-deprived herring gulls. *Comp. Biochem Physiol* 81A:911-913.

# This Month in EHP

By Eddy Ball

The current issue of [Environmental Health Perspectives \(EHP\)](#) is sure to spark a lively exchange of opinion with its featured stories on asbestos. They include a commentary, “The Case for a Global Ban on Asbestos,” companion editorial, and news feature, “A Worn-Out Welcome: Renewed Call for a Global Ban on Asbestos,” along with a related research article, “Respiratory Symptoms in Libby, Montana.”

Mitochondrial disease is the focus of a news story, “Mito-Conundrum: Unraveling Environmental Effects on Mitochondria,” and a research report, “Imaging of Mitochondrial Oxidative Stress.”

This Month’s [Podcast](#) features a discussion on the fetal basis of adult disease with Deborah Cory-Slechta, Ph.D., a professor in the Department of Environmental Medicine at the University of Rochester School of Medicine and Dentistry.

Additional research reports examine Lyme disease, indoor air pollution, and asthma:

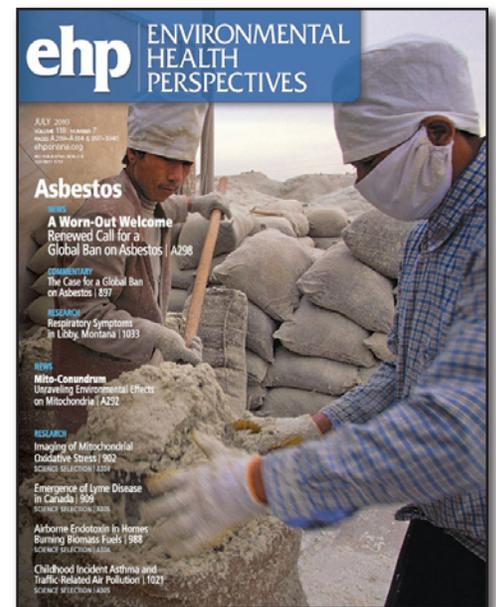
- “Emergence of Lyme Disease in Canada”
- “Airborne Endotoxin in Homes Burning Biomass Fuels”
- “Childhood Incident of Asthma and Traffic-Related Air Pollution”

The August issue of EHP promises to be as timely as the evening news with its examination of dispersants and worker safety in the oil spill in the Gulf.

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<http://twitter.com/ehponline>



# Extramural Papers of the Month

By Jerry Phelps

- [Arsenic-Related Mortality in Bangladesh](#)
- [Flame Retardant Linked to Decreased Thyroid Hormone Levels in Pregnant Women](#)
- [Solutions to Arsenic Groundwater Contamination](#)
- [New Kidney Injury Biomarker](#)



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

## Arsenic-Related Mortality in Bangladesh

NIEHS-supported researchers report that 21.4 percent of all deaths in the Araihaazar region of Bangladesh can be attributed to well water arsenic concentrations greater than 10 micrograms per liter ( $\mu\text{g/L}$ ). Their findings are from the first prospective study to investigate the link between arsenic exposure and mortality and are published online in *The Lancet*.

Current estimates suggest that 35-77 million of the 125 million inhabitants of Bangladesh drink arsenic-contaminated water. More than 55 percent of the 11,746 study participants drink water with more than 50  $\mu\text{g/L}$ , the current Bangladesh standard, and 75 percent consume water which is more contaminated than the World Health Organization standard of 10  $\mu\text{g/L}$ . However, a unique feature of this study is that it includes participants at both the low and high ends of the dose-response curve. For people exposed to the highest doses of arsenic, all-cause mortality was nearly 70 percent higher relative to those exposed to less than 10  $\mu\text{g/L}$ .

Arsenic-contaminated drinking water is an environmental health problem in many parts of the world, including some areas of the United States. The investigators plan follow-up studies to assess other long-term effects of arsenic exposure and how they might be ameliorated by changes in exposure. However, they point out that “solutions and resources are urgently needed to mitigate the resulting health effects of arsenic exposure.”

*Citation:* [Argos M, Kalra T, Rathouz PJ, Chen Y, Pierce B, Parvez F, et al. 2010. Arsenic exposure from drinking water, and all-cause and chronic-disease mortalities in Bangladesh \(HEALS\): a prospective cohort study. \*Lancet\*. Epub ahead of print. doi:10.1016/S0140-6736\(10\)60481-60483. \(\[Story\]\(#\)\)](#)

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## Flame Retardant Linked to Decreased Thyroid Hormone Levels in Pregnant Women

In the largest study conducted to date, researchers at the University of California Berkeley report that exposure to flame retardant compounds is associated with decreased levels of thyroid-stimulating hormone (TSH) around the beginning of the third trimester of pregnancy. The risk of sub-clinical hyperthyroidism was also associated with exposure.

Polybrominated diphenyl ethers or PBDEs are used as flame retardants in a variety of products including textiles, furniture, automobiles, airplanes, and electronics. PBDEs are lipophilic and bioaccumulate in wildlife and humans, and also biomagnify up the food chain. They are found in almost all human beings on earth and their concentration in human serum and breast milk has increased exponentially in the last three decades. They are persistent compounds with half-lives ranging from two to twelve years.

The research team measured PBDE and thyroid hormone levels in 270 pregnant women, most of whom were Mexican American. Lab analyses showed that women with higher levels of PBDEs had lower levels of TSH.

These findings are important because of the important role that maternal thyroid hormone levels play in fetal development. Future studies planned by the team will examine whether subclinical hyperthyroidism and maternal exposure to PBDEs are associated with adverse pregnancy outcomes such as preeclampsia, premature birth, and low birth weight.

*Citation:* [Chevrier J, Harley KG, Bradman A, Gharbi M, Sjödin A, Eskenazi B.](#) 2010. Polybrominated diphenylether (PBDE) flame retardants and thyroid hormone during pregnancy. *Environ Health Perspect.* Epub ahead of print. doi:10.1289/ehp.1001905. ([Story](#))

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## Solutions to Arsenic Groundwater Contamination

According to the World Health Organization, approximately 60 million people living in Bangladesh, or about half the population, drink water contaminated with unsafe levels of arsenic, defined as greater than 10 micrograms per liter. The contamination puts people at high risk for cancer, diabetes, and other serious diseases. A new NIEHS-funded review article examines variations in groundwater arsenic in South and Southeast Asia and makes recommendations for reducing exposures in the region.

In Bangladesh, wells that tap into deep aquifers are typically uncontaminated and provide safe drinking water. However, in recent years, farmers have started to drill deep wells for irrigation, which can compromise access to clean drinking water.

The Himalayan mountain range has rocks and sediments that naturally contain arsenic. As these sediments move downstream, bacteria cause arsenic to be released from the solid material into shallow aquifers.

Because relatively small amounts of arsenic wind up in rice grains grown in irrigated paddies, the authors recommend drawing from shallower wells for irrigation, reserving deep aquifers for drinking, and using filtration to remove arsenic from the water in areas without deep aquifers. The research team also recommends a vigorous, recurring testing program for wells in the region, as well as additional research into the use of rainwater harvesting and filtration.

*Citation:* [Fendorf S, Michael HA, van Geen A.](#) 2010. Spatial and temporal variations of groundwater arsenic in South and Southeast Asia. *Science* 328(5982):1123-1127.

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## New Kidney Injury Biomarker

NIEHS-supported researchers have identified a new biomarker for kidney toxicology that could lead to better and faster diagnosis of kidney injury, with potential applications in the clinical setting as well as in drug development.

Acute kidney injury, including drug-induced toxicity, is a common and often fatal clinical condition with a mortality rate of 40-80 percent in intensive care settings. Nephrotoxicity in animal studies is a major factor in the failure of many candidate drugs because of the lack of precise biomarkers for monitoring early kidney injury.

The research team tested transmembrane tubular protein kidney injury molecule -1 (Kim-1) as a superior marker for kidney injury. Traditional markers of renal injury, such as blood urea nitrogen (BUN), serum creatinine (SCr), and N-acetyl-beta D-glucosaminidase (NAG), lack the sensitivity or specificity necessary to detect nephrotoxicity before considerable loss of function occurs.

The researchers used rat toxicology studies to compare the diagnostic performance of Kim-1 to BUN, SCr, and NAG as predictors of kidney tubule damage scored by histopathology. The results show that Kim-1 outperforms all three of the other markers in multiple rat model of kidney injury. The study authors conclude that Kim-1 measurement will significantly aid the prediction of human kidney toxicity in candidate drugs by early identification and elimination of compounds that are potentially nephrotoxic.

*Citation: Vaidya VS, Ozer JS, Dieterle F, Collings FB, Ramirez V, Troth S, et al. 2010. Kidney injury molecule-1 outperforms traditional biomarkers of kidney injury in preclinical biomarker qualification studies. Nat Biotechnol 28(5):478-485.*

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

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## Intramural Papers of the Month

*By Erin D. Hopper and Tara Cartwright*

- [A Magnesium-Coordinating Threonine Plays a Critical Role in GTPase Catalysis](#)
- [Cell Survival is Modulated by Phosphorylation of SIRT1](#)
- [Nuclear Receptor CAR Represses the Death of Mouse Primary Hepatocytes](#)
- [Stem Cell Survival Advantage Toward Arsenic Drives Malignant Transformation](#)

### **A Magnesium-Coordinating Threonine Plays a Critical Role in GTPase Catalysis**

NIEHS scientists from the Laboratory of Neurobiology have demonstrated the critical role of the Mg<sup>2+</sup>-coordinating Thr residue in the catalytic rate of regulatory GTPases. Mutation of Thr 204 to Gln or Ala did not affect the ability of the G-protein alpha subunit (G $\alpha$ ) to be activated by GTP, but it significantly reduced the rate of GTPase activity.

Gs $\alpha$  contains two switch domains, SWI and SWII, that undergo a conformational change upon Mg<sup>2+</sup> and GTP binding, and this conformational change leads to protein activation. The bound Mg<sup>2+</sup> is coordinated to six oxygens — two from GTP, two from water, one from a Thr residue in SWI, and one from a Ser residue.

Mutation of the Ser residue results in a protein with reduced capacity for binding Mg<sup>2+</sup>, but a dominant action that reduces and even prevents wild type molecules from acting. In contrast, mutation of the Thr residue results in the activation of the SWII domain and a reduction in the rate of GTPase activity.

This study revealed the mechanistic basis for the differences in the effects of mutating the coordinating Ser and Thr residues. Unlike the Ser, the Thr plays a critical role in the catalysis of GTP by Gs $\alpha$ , which it does by helping to move the hydrolytic water molecule into the proper position for catalysis. This feature of catalysis is expected to be common to all regulatory GTPases.

*Citation:* [Zurita A, Zhang Y, Pedersen L, Darden T, Birnbaumer L](#). 2010. Obligatory role in GTP hydrolysis for the amide carbonyl oxygen of the Mg<sup>2+</sup>-coordinating Thr of regulatory GTPases. *Proc Natl Acad Sci USA* 107(21): 9596-9601.

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## Cell Survival is Modulated by Phosphorylation of SIRT1

A study from the NIEHS Laboratory of Signal Transduction and Laboratory of Structural Biology has revealed a new mechanism of SIRT1 regulation that demonstrates the important role of the protein in cell fate.

Two anti-apoptotic members of the DYRK (dual specificity tyrosine-phosphorylated and regulated kinase) family bind and phosphorylate SIRT1. Using mass spectrometry, the authors showed that these two DYRK members, DYRK1A and DYRK3, phosphorylated the Thr(522) residue, resulting in SIRT1 activation.

Activated SIRT1 deacetylates p53, and this deacetylation promotes cell survival. However, the knockdown of DYRK1A and DYRK3 results in the hyperacetylation of p53, resulting in p53 activation. This activation makes cells more sensitive to genotoxic stress and leads to the promotion of stress-induced cell death.

Although SIRT1 has been considered as a possible therapeutic target for cancer, the regulatory network governing SIRT1 activity is not well understood. Whether SIRT1 acts as a tumor suppressor or a tumor promoter may depend on whether the cancer cells express wild type or mutant p53. Further studies may provide insight into the role of p53 in the anti- and pro-apoptotic effects of SIRT1.

*Citation:* [Guo X, Williams JG, Schug TT, Li X](#). 2010. DYRK1A and DYRK3 promote cell survival through phosphorylation and activation of SIRT1. *J Biol Chem* 285(17): 13223-13232.

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## Nuclear Receptor CAR Represses the Death of Mouse Primary Hepatocytes

NIEHS scientists in the Laboratory of Reproductive and Developmental Toxicology have identified the anti-apoptotic factor Growth Arrest and DNA Damage-Inducible 45beta (GADD45B) as a Constitutive Active/Androstane Receptor (CAR)-regulated signaling molecule, through which CAR represses Tumor Necrosis Factor alpha (TNF $\alpha$ )-induced cell death.

To examine the role of the nuclear receptor CAR in cell death, a team of investigators treated primary hepatocytes from *Car*<sup>+/+</sup>, *Car*<sup>-/-</sup>, *Gadd45b*<sup>+/+</sup> and *Gadd45b*<sup>-/-</sup> mice with TNF $\alpha$  and Actinomycin D in the presence or absence of TCPOBOP, the CAR activating ligand. Team members also used GST-pull down and co-immunoprecipitation assays to investigate the protein-protein interactions of CAR with GADD45B and MKK7. Kinase assays determined whether the formation of a CAR protein complex alters the ability of MKK7 to phosphorylate JNK1.

These studies demonstrated that CAR required the presence of an AF2 domain to bind to GADD45B, and that this binding forms a protein complex that inhibits MKK7-dependent phosphorylation of JNK1, repressing the death of TNF $\alpha$ -induced mouse primary hepatocytes. Taken together, these findings provide further insight into the molecular mechanism by which CAR regulates the promotion of HCC development in mice.

*Citation:* Yamamoto Y, Moore R, Flavell RA, Lu B, Negishi M. 2010. Nuclear receptor CAR represses TNF $\alpha$ -induced cell death by interacting with the anti-apoptotic GADD45B. PLoS One 5(4):e10121.

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## Stem Cell Survival Advantage Toward Arsenic Drives Malignant Transformation

Researchers from the National Cancer Institute (NCI) at NIEHS, now with NTP Laboratories, reported that the carcinogen arsenic targets stem cells for transformation, eventually producing cancers enriched in cancer stem cells (CSCs). This is facilitated by a stem cell survival advantage toward arsenic during malignant transformation.

The investigators compared both innate and acquired resistance of the human prostate stem cell line (WPE-stem) with the mature parental nontumorigenic cell line (RWPE-1) following acute (24-72 hours) and chronic (6 weeks) arsenite exposure. Analysis of CSCs included the utilization of holoclone and sphere formation assays, growth in soft agar, and expression of stem cell biomarkers.

WPE-stem exhibited an innate resistance and hyperadaptability to arsenite, including apoptosis, compared to the parental RWPE-1. WPE-stem demonstrated a higher expression of antiapoptotic genes, lower expression of proapoptotic genes, and increased arsenic-induced stress response and arsenic efflux-related genes during transformation.

These observations further strengthen the argument that arsenic most likely targets cells that have either a stem or progenitor phenotype and undergo survival selection during arsenic-induced malignant transformation.

*Citation:* Tokar EJ, Qu W, Liu J, Liu W, Webber MM, Phang JM, Waalkes MP. 2010. Arsenic-specific stem cell selection during malignant transformation. J Natl Cancer Inst. 102(9):638-649.

(Erin Hopper, Ph.D., is a postdoctoral fellow in the NIEHS Laboratory of Structural Biology Mass Spectrometry Group. Tara Ann Cartwright, Ph.D., is a postdoctoral fellow in the NIEHS Laboratory of Neurobiology Membrane Signaling Group.)

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# Inside the Institute

## Ethics Made Easy

By Laura Hall

During Ethics Day on June 10, the NIEHS Office of Ethics showcased its new initiative to help make complying with government ethics regulations easier. Part of the initiative was consolidating the Bioethics Program, which applies to scientific research, into the Office of Ethics to make it easier to meet everyone's ethics needs under one umbrella program.

The goal of the program is to make the ethics regulatory information and forms easier to access, and to welcome and encourage people to ask any questions that they might have. "I don't worry about people who ask questions — I worry about those people who don't ask questions," said NIEHS Deputy Ethics Counselor Bruce Androphy, J.D. "Some of the NIEHS rules are hard to get through, to make sense of, [and] we don't want people being tripped up inadvertently."

The program began making ethics compliance easier by revamping its [Web pages](#) to be a one-stop shop — allowing employees to immediately find what they need. With Ethics Day, the program gave employees the opportunity to meet all the members of the Office of Ethics, learn about ethics rules, and ask questions in an informal setting.

Ethics Day also offered several "Responsible Conduct of Research" training sessions that satisfy the mandatory annual research training requirement for scientists. The other annual mandatory ethics course that all employees must take will be offered later in the year.

Senior Policy Officer Holli Beckerman Jaffe, J.D., of the [NIH Ethics Office](#), and Perry Newson, J.D., the executive director of the [North Carolina State Ethics Commission](#), were the two invited speakers for the brown bag lunch session.

Jaffe explained that ethics regulations are really standards of conduct. "My area is not judgmental, it's just rules," she said. Training, advice, and review are the main parts of the ethics program. "We don't expect you to be experts in the rules after training," she said. "We just want you to have a general idea of when you need to call the ethics office."



Members of the Office of Ethics posed after the Ethics Day sessions. Shown, left to right, are David Resnik, Jackie Stillwell, Stephen Copeland, Androphy, and Patricia Harris. Barbara Morse, the other member of the team, is not pictured. (Photo courtesy of Steve McCaw)



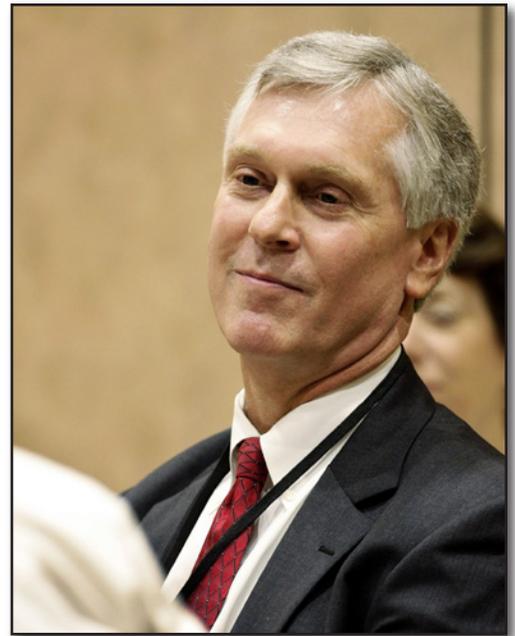
Androphy, left, and Jaffe shared a light moment with the other participants in the relaxed atmosphere of the brown bag lunch. (Photo courtesy of Steve McCaw)

It is important to find out what the rules are because federal employees can be subject to criminal prosecution if they break certain ones. “Within our program, if you violate a criminal statute, we can’t undo that,” explained Jaffe. “Ethics is not an area in which you act first and then beg forgiveness,” added NIEHS/NTP Director Linda Birnbaum, Ph.D., during the brown bag lunch.

Newson discussed how North Carolina state government ethics regulations evolved. He said, “The primary motivating factor for ethics regulation in this country is scandal.” Newson pointed out similarities between North Carolina and federal ethics regulations. He agreed with Jaffe that ethics is “rules and regulations and laws, many of which are definitely counterintuitive.” He also does not expect North Carolina government employees to know the rules. “They just have to be aware enough — and this is where the training comes in — to know that this is something that they need to ask a question about.”

Androphy introduced the speakers at the brown bag lunch and talked about ethics at NIEHS in the second general ethics session. He went over some of the ethics rules that commonly pertain to NIEHS staff, such as the gift rules. He also covered the conflict of interest rules that could result in criminal prosecution if not followed correctly. “My goal is to keep people out of trouble,” said Androphy. His motto for the Institute is “Be early, be accurate, and be ethical.”

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



*According to Newson, the State Government Ethics Act enacted in August 2006 was a “perfect storm of ethics reform,” resulting from highly visible profile scandals of state government figures. (Photo courtesy of Steve McCaw)*



*Philip Guzman, J.D., right, director of the North Carolina Central University (NCCU) Public Service Program, and Shawn McKenna, J.D., director of Legal Recruitment at the NCCU Law School, took time out of their day to come and hear about the NIEHS ethics program. (Photo courtesy of Steve McCaw)*



*Rajendra Chhabra, Ph.D, above, is a celebrity, Newson told the other brown bag lunch attendees. Chhabra, who is the NIEHS group leader of the General Toxicology Group, served on the North Carolina Board of Ethics from 1998-2006. The Board of Ethics is the predecessor of the North Carolina Ethics Commission where Newson currently works. (Photo courtesy of Steve McCaw)*



*In her introduction of Androphy, Birnbaum said, “Bruce has really had an impact in our whole ethics approach. This year... we’ve had 100 percent compliance with, for example, getting some of our confidential financial information in, and that involved hundreds of people.” (Photo courtesy of Steve McCaw)*

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## Celebrating Friends and Family Day

*By Laura Hall*

Friends and Family Days have always been hot, but this year’s event on June 23 broke the record for NIEHS. The blistering 99 degree heat and Code Orange air quality — unhealthy for sensitive groups — resulted in the cancellation of the afternoon softball competition and drove many of the contests indoors. Nevertheless, the sweltering heat did not stop the fun — or the celebration of Asian and Pacific Islander Heritage.

NIEHS/NTP Director Linda Birnbaum, Ph.D., welcomed the celebrants and explained that this year, Friends and Family Day was combined with the NIEHS Asian and Pacific Islander Heritage Month commemoration. She urged the attendees to sample the ethnic food, view the exhibits, and enjoy the music of the traditional Japanese Taiko Drummers, as well as take part in the games and play.

## Where Do the Federal Ethics Rules Originate?

When questioned about who writes the rules, Jaffe explained. “The criminal statutes are written by Congress and many go back to the Civil War.” The rule that a federal employee cannot represent another person back to the government — such as talking to the Internal Revenue Service on behalf of a neighbor, for example — is one of those civil war rules that still apply to all federal employees.

Other rules are written by the U.S. Office of Government Ethics (OGE), which was established by the Ethics in Government Act passed in 1978. [Financial disclosure regulations](#) are one set of OGE rules. Another set, the government-wide standard of conduct regulations, includes the [gift rules](#).

A third source of rules is the U.S. Department of Health and Human Services (HHS). Its rules are applicable strictly to the HHS or just to the NIH. They include the [outside activity regulations](#) and the regulations that place a limit on the value of pharmaceutical and biotechnology company holdings for senior NIH people.

Birnbaum also cautioned everyone about the heat. “It’s so hot today. It is also a Code Orange day, which means you shouldn’t exert yourself too much outside,” she said.

However, no degree of heat was going to stop the popular cake walk.

While the 23 cakes remained cool inside, the many contestants walked on the patio under tents hoping they would win one. The game is somewhat like musical chairs — music is played while the contestants walk around over numbered patio paving squares. When the music stops, those on numbered squares have a chance to win a cake if the number they are standing on is the same one pulled out of a container.

Outside, the children enjoyed the sprinkler and wading pools of water. The goose egg hunt was open to adults, but eagle-eyed children found the eight plastic eggs hidden in the bushes within the planters surrounding the patio. Each child won a prize and uncovered a fact about the lake. At the lake itself, catch-and-release fishing was the featured activity.

There were also booths for face painting, party hats, and the Environmental Protection Agency, which, ironically, displayed electron microscope pictures of various air pollutants.

The competitive spirit came out in the bingo games as well as the limbo and hula hoop contest. Gary Bird, who emceed the contests, also encouraged people to take part in karaoke. In all, there were many happy prize winners.

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



*“We’ve had to postpone the softball game which many of us were really looking forward to. It is just too hot,” said Birnbaum. “Any of the outside activities today are water related.” (Photo courtesy of Steve McCaw)*



*Bill Jirles, center, has obviously made a trip to the hat-making booth. His children are firing their water pistols while they cool off in one of the wading pools set out on the patio to provide some heat relief. (Photo courtesy of Steve McCaw)*



*Rocky Iwashima performs traditional Japanese Taiko drumming. Invited to help celebrate Asian and Pacific Islander Heritage Month, he and his wife, Yoko Iwashima, are two members of the local Triangle Taiko group. The celebration of Friends and Family Day and Asian and Pacific Islander Heritage Month were combined this year. (Photo courtesy of Steve McCaw)*



*Chris Long, left, paints a design on the arm of a young girl, center, as mom Ritu Rana helps out. Long considers himself an experienced face painter. "With a son and daughter now in their 20s, I've painted many a face at birthday parties," he said. (Photo courtesy of Steve McCaw)*



*Clyde Hasty, center, proved he was a serious contender in the hula hoop marathon, as Dona McNeill cheered him on. (Photo courtesy of Steve McCaw)*



*This quartet, made up of daughters of employees and family friends, had a great time singing a favorite song, "Party Girl" by Miley Cyrus, during their karaoke session. After allowing others a turn, they came back for another song. (Photo courtesy of Steve McCaw)*

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# NIEHS — A Pioneer in Sustainability and Green Government

By Laura Hall

Three NIEHS employees accepted the U.S. Department of Health and Human Services (HHS) 2009 Organization Green Champion Award June 10 on behalf of the many members of the NIEHS family who have worked for environmental sustainability over several decades ([see the NIEHS Sustainability Report](#)).

Deputy Associate Director for Management Chris Long, NIEHS Sustainability Coordinator Trish Castranio, and NIEHS Environmental Awareness Advisory Committee (EAAC) co-chair Dick Sloane were pleased with the honor and the opportunity to exchange war stories with other sustainability awardees. “It was a good opportunity to enjoy the fruits of all our hard work and be grateful for having an institute that cares enough to work so hard to make changes,” said Castranio.

This is the first time HHS has given this award to an entire organization, honoring employees at NIEHS for their commitment to [environmental stewardship](#) ([see related story](#)). In addition, the NIEHS Facilities and Management Branch won the 2009 Green Champion Energy and Water Award for its conservation initiatives and use of innovative contracting.

One of the reasons that NIEHS stands out is that many of the top 10 ideas in each of the six sustainability categories of the White House [GreenGov Challenge](#) — ways to conserve energy and water, eliminate waste and reduce carbon emissions, and incorporate sustainability in government buildings, products, and purchases — have already been implemented at the NIEHS, some decades ago.

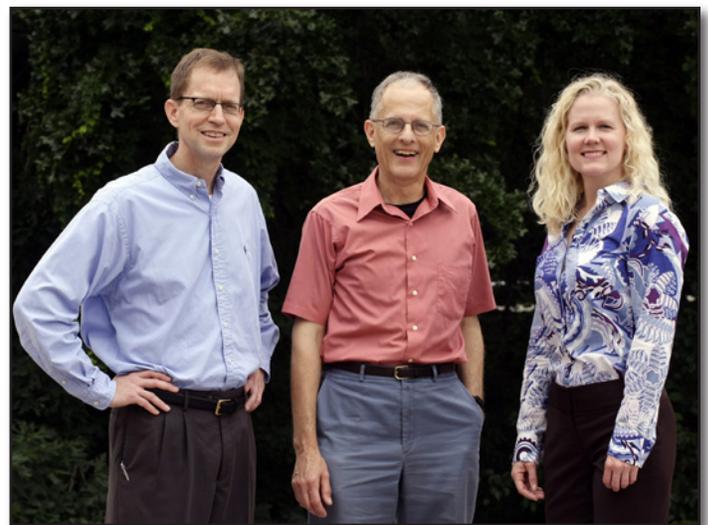
Even years ago, the NIEHS administration was willing to change “normal” practices to lessen environmental impact. Employees volunteered their time to discover viable alternatives to existing practices to make NIEHS more environmentally friendly.

## EAAC

The practice of helping out wildlife, which continues to this day, started in the 1970s with the building of bluebird houses to help the campus bluebird population ([see related story](#)). However, NIEHS environmental sustainability was jumpstarted in April 1990, when the NIEHS Office of Management formed the EAAC to advise Institute management on environmental issues and to formulate action plans to mitigate any adverse effects arising from day-to-day operations.



*NIEHS plans for wildlife habitat and protection even down to the road signs. By the traffic circle in the main entryway, three wildlife habitat zones can be seen — mowed, meadow, and wooded areas. The sign warns drivers to be on the lookout for some of the resident campus geese that often wander from the mowed areas onto the roadways. (Photo by Laura Hall)*



*Shown left to right, Chris Long, Dick Sloane, and Trish Castranio traveled to Washington, D.C., to accept the Organization Green Champion Award for the NIEHS. “We’re extremely proud that NIEHS won the award, and that we were chosen to accept it,” said Long. “Trish, Dick, and I all feel that we were just the messengers representing hundreds of current and former NIEHS staff.” (Photo courtesy of Steve McCaw)*



*In 2009 the NIEHS recycled 407,196 pounds of materials — 49 percent of our annual generated waste. Sloane was the project officer for many earlier latest recycling projects, as well as the latest one — composting post-consumer cafeteria food waste and utensils, which was implemented in 2009. (Photo courtesy of Steve McCaw)*



*Facility Operations Branch employee Dennis Will, seated in car, and Electrical Technician Jim McDonough make daily use of the NIEHS electric car acquired in 2002 to travel between the campus support buildings such as the Warehouse and main building. “It’s very handy,” said McDonough, who transports laboratory equipment needing repair. (Photo by Laura Hall)*

Then NIEHS Associate Director for Management Charles Leasure, Jr., tapped former NIEHS principal investigator Robert Chapin, Ph.D., a self-described “lunatic eco-left fringe wing-nut,” to head the committee. Approximately 30 employees, representing every program area and operational division within NIEHS, were on the committee. One of their goals was to recycle all possible materials.

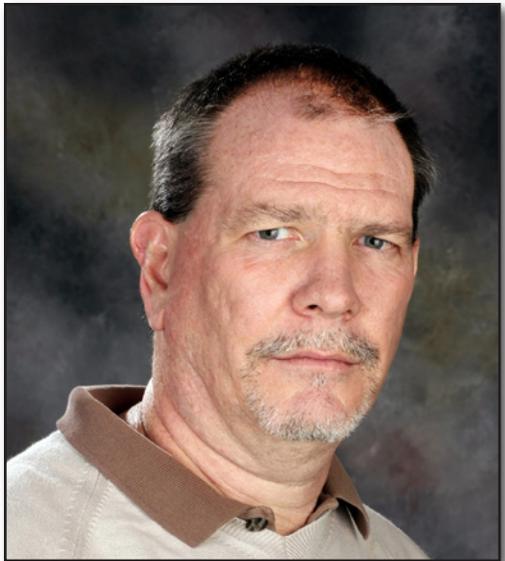
“It really boiled down to the enthusiasm of the people involved,” Chapin said recently. “I set a tone and managed to recruit and inflame folks with lots of internal energy, and then got the heck out of their way, and off they went.”

In 1993, the NIEHS began its formal, award-winning recycling program. Since 1993, the Institute has recycled 11,600,000 pounds of many different materials. Sloane, formerly the NIEHS resource recovery specialist, was involved in finding ways to recycle the various materials.

“Dick, in many ways, set the standard for the Triangle area,” said Long, whose former position at the neighboring Environmental Protection Agency (EPA) campus was managing the design and construction of EPA green buildings. “At EPA, we used Dick Sloane as a green benchmark. There were literally many times we asked, “What would Dick do?”

**E-Con**

In 2007, during the worst drought in North Carolina history, the critical need to reduce water use galvanized different groups across the Institute and our EPA neighbors to coalesce into one group, the Water Crisis Task Force (WCTF). The WCTF, headed by Operations and Security Branch Chief Mitch Williams, identified and coordinated implementation of water conservation measures. The WCTF renamed itself E-Con in early 2009 when it took on the additional role of energy conservation ([see related story](#)).



*“The WCTF proved highly successful in reducing water use on the federal campus and in carrying forward some of these lessons into the newly leased NIEHS Keystone facility,” said Williams, who headed the WCTF workgroup. (Photo courtesy of Steve McCaw)*

Along with a willingness to find ways to do things a little differently, what pushes our Institute ahead of the pack is the dedication of NIEHS employees, as well as a management team that is willing to listen and implement good ideas.



*Long, front row center in blue, posed with some of the many other members of the NIEHS family who have all contributed to environmental sustainability at the Institute. Long said of his work with the NIEHS team, “Sustainability is in my DNA.” (Photo courtesy of Steve McCaw)*

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

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## Hawk Calls NIEHS Home

*By Eddy Ball*

On a hot afternoon in mid-June, photographer Steve McCaw aimed his telephoto lens at a beautiful hawk that apparently is nesting next to the main building on the NIEHS campus in Research Triangle Park, N.C. McCaw was acting on a tip from NIEHS employees James Huff and Frank Johnson.

Although more than 100 species of birds have been sighted on the 500-acre campus shared by NIEHS and the U.S. Environmental Protection Agency, few command the respect of the hawk. In one shot, it appears the hawk is diverting attention from her nesting brood, and McCaw admitted afterwards, “I was hoping that she wouldn’t use her talons on me” as he tried to get as close as possible.



*The hawk posed in front of the NIEHS sign on the main building on the afternoon of June 16. (Photo courtesy of Steve McCaw)*

Whether the hawk would have attacked, no one can say. One thing, however, is clear — the people who know about her are proud she’s decided to call NIEHS home... at least until her aerie of chicks can fend for themselves.



*From the detail of this close up, it's easy to see why McCaw felt a bit talon-shy as he shot the photos. (Photo courtesy of Steve McCaw)*



*A bystander told McCaw that the hawk might be diverting attention from her nearby nest of chicks. (Photo courtesy of Steve McCaw)*

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Environmental Health Sciences

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

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