

## NIEHS Spotlight



### Symposium Highlights Age-Related Issues and Research

In an effort to help the NIEHS community better understand the changing demographics of aging and emerging patterns of chronic disease among seniors, the NIEHS Diversity Council Disability Advocacy Committee (DAC) presented a mini symposium October 30 with experts in the fields of aging research and senior care. ...[read more](#)



### Young Investigator Honored at White House Ceremony

NIEHS grantee Sven-Eric Jordt, Ph.D., already had plenty to be proud of as he joined 55 other young researchers at the White House November 1 for an awards ceremony. ...[read more](#)



### Summer Intern Presents at Bioinformatics Conference

When Venus Welch came to NIEHS to work in the 2007 Summers of Discovery program, she had no idea that five months later she would be addressing experts in toxicogenomics and bioinformatics at the First International Conference on Toxicogenomics Integrated with Environmental Sciences (TIES). ....[read more](#)



### Trainees and Investigators Shine at Fifth Annual Science Day

Now in its fifth year, the NIEHS Annual Science Awards Day is a fall tradition for the Division of Intramural Research. The event celebrates the scientific achievements of investigators and trainees with a full day of oral presentations and poster sessions. ...[read more](#)

## Science Notebook



### Michael Kastan Gives Falk Memorial Lecture

In Rodbell Auditorium on November 8, Michael B. Kastan, M.D., Ph.D., became the twenty-third scientist to give the NIEHS Hans L. Falk Memorial Lecture, an annual seminar that features a researcher who has made significant contributions to environmental health sciences research. ...[read more](#)



### GEMS Marks Quarter Century at Annual Fall Meeting

The Genetics and Environmental Mutagenesis Society (GEMS) celebrated 25 years of bringing together the area's junior investigators, trainees and veteran investigators at its 2007 Fall Meeting in Research Triangle Park. ...[read more](#)



### Superfund Grantee Shares "Lessons from the Wild"

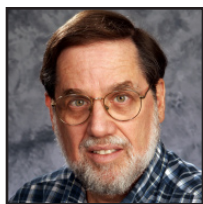
In his work as director of the Superfund Basic Research Program at Duke University, Toxicologist Richard Di Giulio, Ph.D., combines evolutionary theory, ecology, basic biology and toxicology into a research approach he describes as "evolutionary toxicology." ....[read more](#)



### Using Gene Expression for Early Detection of Acetaminophen Overdose

In a new study, researchers report they could detect toxic levels of acetaminophen in laboratory animals by analyzing gene expression in the blood. This NIEHS-funded study could be a first step in developing accurate new tools to detect acetaminophen overdose in humans. ...[read more](#)

## NIEHS Spotlight



### Melnick Receives 2007 APHA Rall Award

National Toxicology Program Toxicologist Ron Melnick, Ph.D., found himself in good company at the November 6 Awards Ceremony held by the American

Public Health Association (APHA) during its 135th Annual Meeting in Washington, DC. ...[read more](#)



### New Editor-In-Chief for Environmental Health Perspectives

Hugh A. Tilson, Ph.D. a nationally recognized environmental health scientist, has been named the new

editor-in-chief of Environmental Health Perspectives (EHP), a journal published by NIEHS. Tilson will start at NIEHS Nov. 26, 2007 and will officially begin his new role as editor-in-chief January 1, 2008. ...[read more](#)



### NIEHS Engages Environmental Health Challenges in Asia

Acting Deputy Director Bill Suk, Ph.D., traveled to Bangkok, Thailand for the 6th Princess Chulabhorn International Science Congress (PC VI) November

26 – 29. The conference was his third meeting on the continent this fall as part of NIEHS engagement of environmental health challenges in the developing countries of Asia. ....[read more](#)

## Science Notebook



### Conference Promotes Bioinformatics in Genomics Fields

NIEHS is helping to open new lines of interdisciplinary communication with its sponsorship of the first in a series of international conferences emphasizing the application of bioinformatics in the fields of toxicogenomics and environmental genomics. ...[read more](#)

### New ONES Grantees to Visit Institute in January

This year's seven Outstanding New Environmental Sciences (ONES) awardees will visit NIEHS on January 7, 2008 to meet NIEHS staff and make presentations about their work. The ONES awardees will receive five-year grants totaling \$3.5 million to support direct costs, equipment and other resources. ...[read more](#)



### Upcoming Distinguished Lecture Features Errol C. Friedberg

The 2007-2008 NIEHS Distinguished Lecture Series continues at 11:00 a.m. on December 11 with a talk by Errol C. Friedberg, M.D., titled "Specialized DNA Polymerases in Higher Organisms: Insights from the *Polk* Knock-Out Mouse." ....[read more](#)

## Inside the Institute



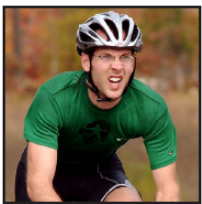
### Employees Mix and Mingle at Nottingham

It didn't take long for most people at the Institute's first Mix and Mingle session in Nottingham Hall November 14 to see the wisdom behind the new series of get-togethers initiated by NIEHS Acting Director Sam Wilson, M.D. ...[read more](#)



### Cherokee Historian Gives Heritage Month Talk at NIEHS

Eastern Band of the Cherokee historian and Welcome Center representative Buck West shared his personal and tribal history with NIEHS staff during a Native American Heritage Month lecture November 14. ...[read more](#)



### O'Fallon Competes in World Championship

People who think that even world-class athletes need a break after a tough competition haven't yet talked to NIEHS Program Administrator Liam O'Fallon. ....[read more](#)

## Extramural Research

### Extramural Update

This year marks the 20th Anniversary of the establishment of the two NIEHS Superfund programs, the Superfund Basic Research Program (SBRP) and the Worker Education and Training Program (WETP). NIEHS plans two anniversary celebrations of the programs, which were created under the Superfund Amendments and Reauthorization Act of 1986. ...[read more](#)

### Extramural Papers of the Month

- [Age-Related Cognitive Decline and Lead Exposure](#)
- [Have Particulate Air Pollution Regulations Affected Mortality Risks?](#)
- [Statin Drugs Maintain Lung Function in the Elderly](#)
- [Polymorphisms in Nucleotide Excision Repair Genes and Breast Cancer Risk](#)

## Intramural Research

### Intramural Papers of the Month

- [Identification of a New Base Excision Repair Cofactor](#)
- [A Novel Mechanism for Integrating Inositol Phosphate Signaling Pathways](#)
- [Hydrophobicity is Necessary in nAChR Signaling](#)
- [The Role of Accessory Proteins in Translesion DNA Synthesis](#)

## Calendar of Upcoming Events

- **December 3 – 5 (Off-site)** at Washington Duke Inn, Durham, 8:00 – 5:00 — “Superfund Basic Research Program: 20 Years of Success and a Vision for the Future”
- **December 5**, in D250, 2:00 – 3:00 — Robert Rice, Ph.D., speaking on “Suppression of insulin effects, protein kinase C action and Notch1 signaling by arsenic.”
- **December 6**, in Rodbell Auditorium, 8:00 – 5:00 — NTP Board of Scientific Counselors
- **December 6**, in Building 101 Mall, 7:30 – 3:00 — Holiday Craft Fair
- **December 7**, in Rodbell Auditorium, 9:00 – 10:00 — Frontiers in Environmental Sciences Lecture Series, featuring H. T. Banks, Ph.D., topic TBA
- **December 7**, in Rodbell C, 11:00 – 12:00 — LRDT Seminar Series: Jeanne Wilson-Rawls, Ph.D., speaking on “Notch signaling in folliculogenesis and gonadal development”
- **December 10 - 12 (Off-site)** at Park Plaza Hotel, Boston, 8:00 – 5:00 — Environmental Justice Grantee Meeting
- **December 11**, in Rodbell Auditorium, 11:00 – 12:00 — Distinguished Lecture Series with Errol C. Friedberg, M.D., speaking on “Specialized DNA Polymerases in Higher Organisms: Insights from the *Polk* Knock-Out Mouse”
- **December 12**, in Rodbell Auditorium, 7:30 – 3:00 — Blood Drive
- **December 13**, in F193, 10:30 – 11:30 — LPC/LMT Seminar Series with Bruce J. Aronow, Ph.D., speaking on “Exploring Biological Systems Network Structures and Functions Responsible for Development, Homeostasis, and Disease”
- **December 14**, in Rodbell Auditorium, 9:00 – 10:00 — Frontiers in Environmental Sciences Lecture Series, featuring Sharon Hrynkow, Ph.D., topic TBA
- View More Events: [NIEHS Public Calendar](#)

# NIEHS Spotlight

## Symposium Highlights Age-Related Issues and Research

By Robin Arnette

In an effort to help the NIEHS community better understand the changing demographics of aging and emerging patterns of chronic disease among seniors, the NIEHS Diversity Council Disability Advocacy Committee (DAC) presented a mini symposium October 30 with experts in the fields of aging research and senior care. “The Science of Aging,” held in Rodbell Auditorium, was co-sponsored by NIEHS and the National Institute on Aging (NIA) and chaired by DAC member Alicia Moore, a biologist in the Cellular and Molecular Pathology Branch at NIEHS.

The symposium’s morning session was moderated by Darryl Zeldin, M.D., a senior investigator in the Laboratory of Respiratory Biology, and featured Family Care Advisor Angela Reynolds along with four specialists in aging and medicine from NIA. The afternoon session, moderated by Samuel Wilson, M.D., acting director of NIEHS, included presentations by two scientists from the NIEHS Epidemiology Branch and a roundtable discussion.

In her opening remarks, Moore set the tone for the symposium. “We will learn about health and aging in our society, as well as how the environment influences the development and progression of human disease,” she stated. “Today’s symposium attempts to carry out the NIEHS mission—to gain insight on how to reduce the burden of human illness and disability.”

Following Reynolds’ talk on the personal aspects of senior care ([see text box](#)), NIA Research Scientist Kushang Patel, Ph.D., opened the NIA portion of the scientific sessions with a talk on the demographics of aging. He said that the data generated by studies in population aging research are important since the country’s population is not only becoming older, but also racially and ethnically diverse. “Because poverty rates and education level are strong predictors of health status in old age,” Patel said, “minority groups are more likely to experience poor health compared to non-Hispanic whites.”



*According to Moore, the seminar was inspired by findings that “shrinking ratios of workers to pensioners and people spending a larger portion of their lives in retirement are increasingly straining existing health and pension systems.” (Photo courtesy of Steve McCaw)*



*Morning session chair Zeldin, right, monitored questions following Reynolds’ presentation. Reynolds works with for the private sector **A Place for Mom**, which offers free consultation on assisted living options and caregiver support. (Photo courtesy of Steve McCaw)*

The majority of the talk by Epidemiologist Eleanor Simonsick, Ph.D., focused on mobility limitation in older adults because “as rates of dementia increase, the rates of mobility limitation increase as well.” Her research found that minimal exercise—walking a couple of blocks a day over a year’s time—allowed older adults to maintain their walking ability.

Senior Investigator William Ershler, M.D., focused his research on determining the mechanisms involved in frailty, and the results suggested that inflammatory responses are at the root of the condition as he defined its criteria. “Levels of certain cytokines decrease with age, such as interleukin-2 (IL-2) and IL-12, while some increase with age, such as IL-6 and IL-10,” Ershler explained. “Everything from function to mortality is associated with inflammatory proteins.”

According to Senior Investigator E. Jeffrey Metter, M.D., the prostate is a pertinent topic for research in aging because prostate specific antigen (PSA) values—a screening test for prostate health—increase with age and as men develop diseases of the prostate. In 1992 Metter and colleagues at Johns Hopkins University began looking at PSA values in serum samples taken from men who participated in the Baltimore Longitudinal Study of Aging.

During the afternoon session, NIEHS Pre-doctoral Fellow Martha Montgomery reported on her research into the effects of age and environmental exposure on the development of age-related macular degeneration (AMD) among farm workers who applied pesticides and participated in the [Agricultural Health Study](#). “Applicators over 60 years old who were exposed to pesticides, specifically organochlorine and organophosphate insecticides, had increased odds of getting AMD,” Montgomery said. “These associations were not observed in people under 60.”

## “Negotiating the Senior Care Maze” Angela Reynolds’ Tips on Easing the Burdens of Finding Assisted Care

“What I’ve learned from working with thousands of families is that the best thing you can do is be educated early,” Reynolds said at the beginning of her presentation. “Because when you’re in the middle of a crisis and you start to learn about these options, you make snap decisions... [and] you end up choosing things you might otherwise not have chosen.”

To get ready for the enormous responsibilities and expenses of helping a family member who needs assisted care, Reynolds recommends getting a head start:

- Face the facts — according to Reynolds, 95 percent of people aged 45 to 60 whose parents are still alive will find themselves at some point searching for senior care. Depending on the level of assistance involved, residential senior care can cost between \$1300 and \$5000 per month.
- Know the options — too many people don’t understand what is available. Options range from home care, independent living communities and residential care to specially designed, dementia-specific communities and skilled nursing facilities.
- Plan ahead legally and financially — Draw up powers of attorney, living wills and medical health directives, and know where to locate personal and financial records. Learn about the benefits available through insurance, Medicare, Medicaid and the [Department of Veteran Affairs’ pension programs](#).
- Visit facilities and ask lots of questions of the staff and, especially, the residents. Conditions change constantly, and most facilities have waiting lists. Prior to the visits, prepare a list of questions to ask.
- Take advantage of free resources available from non-profit and for-profit organizations.
- Care for yourself and accept help — caregivers experience high levels of stress that actually can damage health. The best caregiver is a healthy caregiver, so don’t try to do it all alone. Take advantage of support groups.

Lou Gehrig's disease or Amyotrophic Lateral Sclerosis (ALS) is a rare neurodegenerative disorder. [Studies](#) led by NIEHS Staff Scientist Freya Kamel, Ph.D., determined that environmental exposures such as smoking, head injury and self-reported occupational lead exposure were associated with increased risk of ALS.

The roundtable discussion at the end of the symposium concluded that several areas of research, for example, studying environmental exposures *in utero* to age 70, could further scientific understanding of the mechanisms of aging.



Afternoon session chair Wilson underscored the importance of trans-NIH collaborations and pointed to the interests of NIEHS in the diseases of aging. Gene-environment interactions are important to development of disease at any age, but they are most telling in the later decades of life. (Photo courtesy of Steve McCaw)



Simonsick, right, joined NIA colleague Ershler at the podium during his question-and-answer session. Biomedical investigations and epidemiological studies converged with Ershler's reference to the famous quip by Eubie Blake: "If I'd known I was going to live this long, I would have taken better care of myself." (Photo courtesy of Steve McCaw)



Shown during the roundtable session, physician-scientist Metter discussed findings of the Baltimore Longitudinal Study of Aging as NIA colleague Patel watched. (Photo courtesy of Steve McCaw)



NIEHS Fellow Montgomery, left, and her mentor, Kamel, have used the statistical power of the longitudinal Agricultural Health Study with its cohort of 89,000 subjects to shed light on the diseases of aging. A substantial percentage of the subjects, enrolled between 1993 and 1997, are at retirement age or quickly approaching it. (Photo courtesy of Steve McCaw)

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# Young Investigator Honored at White House Ceremony

By Eddy Ball

NIEHS grantee Sven-Eric Jordt, Ph.D., already had plenty to be proud of as he joined 55 other young researchers at the White House November 1 for an awards ceremony. By the end of the event, the young investigator had yet another honor to his credit — one of the prestigious 2006 Presidential Early Career Awards for Scientists and Engineers (PECASE) for his outstanding research on the effects of environmental irritants in airway diseases and inflammation.

Established in 1996, PECASE recognizes young scientists the White House considers “the most promising researchers in the Nation within their fields.” Jordt was one of only twelve young scientists employed or funded by NIH to be honored with this year’s PECASE in a ceremony presided over by John H. Marburger III, science advisor to the President and director of the White House Office of Science and Technology Policy.

In a statement about Jordt and the other [NIH recipients](#), NIH Director Elias Zerhouni, M.D., expressed the agency’s confidence in their future contributions to the NIH mission. “We look forward to continued innovation from these outstanding investigators,” he wrote, “as they push the frontiers of medical research during this pivotal time for scientific discovery.”

An assistant professor in the [Department of Pharmacology at the Yale University School of Medicine](#), Jordt enjoys the distinction of being the first NIEHS extramural grantee to receive this honor. He was one eight young investigators awarded the first Outstanding New Environmental Scientist (ONES) grants in 2006, the first year these grants were offered by NIEHS.

The highly competitive ONES awards are designed to offer outstanding scientists who are in the early, formative stages of their careers a strong foundation for their research with a program of R01 research grants for direct costs, equipment and other resources for up to five years. Totaling \$3.6 million in 2006, the grants are administered by the Cellular, Organ and Systems Pathobiology Branch of the NIEHS Division of Extramural Research and Training.

Jordt was awarded his ONES grant for his investigations into the way certain airborne pollutants interact with sensory nerve cells in order to produce eye, nose and throat irritation. His lab uses pharmacological, molecular, genetic and physiological approaches, as well as fluorescent imaging techniques, to investigate the properties of ion channel proteins that serve as sensors for temperature and noxious stimuli in sensory neurons.

Jordt received his undergraduate education in biochemistry in Germany at the Free University in Berlin and his doctorate at the Center for Molecular Neurobiology in Hamburg. He was a postdoctoral fellow at the University of California at San Francisco from 1998 to 2005 and held a Fellowship with the [German Academy of Natural Scientists, Leopoldina](#), prior to joining the faculty at Yale.

As a PECASE winner, Jordt joins an elite group of two at NIEHS. In 2002, intramural Principal Investigator Marilyn Diaz, Ph.D., of the Laboratory of Molecular Genetics, became the first NIEHS scientist to receive the honor.



*Jordt discussed the mechanism of ion channel proteins during his October 2006 ONES presentation, “TRPA1 Channels in Sensory Neurons as Targets for Environmental Irritants.” (Photo courtesy of Steve McCaw)*

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# Summer Intern Presents at Bioinformatics Conference

By Eddy Ball

When Venus Welch came to NIEHS to work in the 2007 Summers of Discovery program, she had no idea that five months later she would be addressing experts in toxicogenomics and bioinformatics at the First International Conference on Toxicogenomics Integrated with Environmental Sciences (TIES). Held October 25 – 26 at North Carolina State University, TIES highlighted cutting-edge research that ties together the two disciplines in an effort to maximize the utility of alternative assessment methodologies.

The conference also featured four student presenters chosen as especially promising by their mentors. Welch was one of them, presenting a study titled “Microarray Gene Expression Reveals Biological Pathways Perturbed in 1, 2- and 1, 4-Dichlorobenzene Hepatotoxicity” and taking home an award of \$200 for her performance.

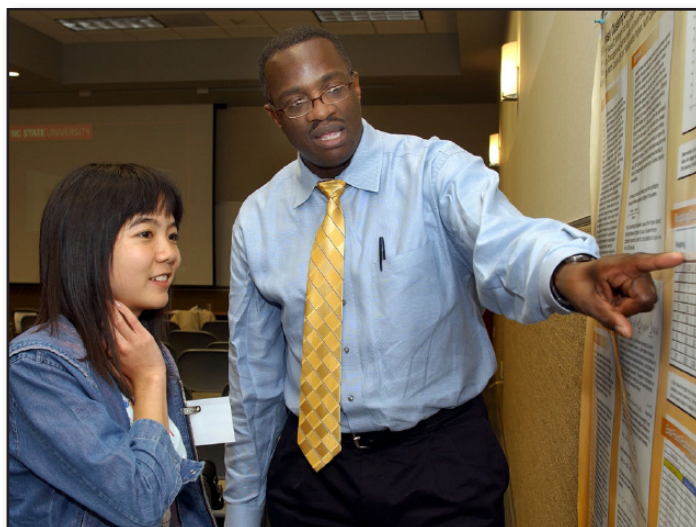
Welch is a doctoral candidate in integrated biosciences with a focus in environmental toxicology and toxicogenomics at Tuskegee University. When she began her internship, she was well grounded in biology, but readily admitted that the world of bioinformatics was “way outside my comfort zone.” Welch was fortunate enough to spend her summer of discovery under the mentorship of Pierre Bushel, Ph.D., NIEHS bioinformatics manager and a member of the TIES 2007 Organizing Committee ([see story in Science Notebook](#)) and to work with Molecular Pathology Group Guest Researcher Gary Boorman, Ph.D.

With Bushel’s help, Welch spent the summer engaged in a crash course on microarray gene expression analysis and the principles of bioinformatics, completing the first drafts of the study she presented at TIES before she returned to Tuskegee for the fall semester. “Pierre was extraordinarily encouraging and patient,” she recalled. “He helped me understand the basics of bioinformatics and how to apply it to research.”

The TIES conference was her first experience making a presentation to senior colleagues as a graduate student, and Welch said she was intimidated by the thought of facing a roomful of experts from around the world, especially the statisticians in the audience.



*Welch was well-organized and poised during her TIES presentation. In her Summers of Discovery internship, Welch took advantage of the program’s weekly seminars on scientific topics as well as workshops on making scientific presentations. “[Coordinator] Charle [League] does a very job planning the summer program,” she noted. (Photo courtesy of Steve McCaw)*



*Bushel explained data on one of his posters displayed at the conference to a student attendee. He was lead author on the study “Simultaneous Clustering of Gene Expression Data with Clinical Chemistry and Pathological Evaluations Reveals Phenotypic Prototypes” and co-author on two others with investigators in the NIEHS Microarray Group. (Photo courtesy of Steve McCaw)*

As it turned out, Welch was amply prepared for the questions she was asked at the end of the talk. She presented her study a second time at the Southeast Regional Collegiate Environmental Science and Health Symposium sponsored by the Centers for Disease Control and Prevention November 14 in Atlanta and felt even more confident when she faced the audience there.

Welch plans to apply for the 2008 summer program and build on last summer's work in bioinformatics. She is now in the process of preparing a proposal to expand on her microarray studies for her dissertation.

Welch took away an important lesson from her experience at NIEHS, one that is sure to impact the direction of her professional life as a student, postdoctoral fellow and environmental sciences investigator. "The key thing I learned last summer with Pierre was the importance of accurate statistical and data analysis," she explained. "Without successful analysis, bench top research really can't be properly applied."

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## Utilizing Microarray Data in Liver Toxicity Studies

Venus Welch's study, "Microarray Gene Expression Reveals Biological Pathways Perturbed in 1, 2- and 1, 4-Dichlorobenzene [DCB] Hepatotoxicity," is the type of research investigators will be performing with compounds as toxicology studies increasingly take advantage of the marriage between omics methodologies and bioinformatics.

Welch's objective was to determine the differences in gene expression patterns and biological pathways between two isomers used in pesticides. 1, 2 DCB is used in potent herbicides, while a less harmful isomer, 1, 4, DCB, is found in mothballs and toilet deodorant blocks.

Welch analyzed the data from assays of the livers of male Fisher rats that received various levels of oral dosing of the two isomers. She also made clinical chemistry measurements of ALT and AST enzymes and histopathology observations of liver tissue.

Anchoring gene expression to sample phenotypes with end-point measurements, Welch determined the central regulating role of tumor necrosis factor and identified gene expression patterns related to apoptosis, MAP kinase signaling and metabolism in the liver. She also identified another key enzyme that is differentially expressed between the pathways of the isomers of DCB.

Building on this kind of information, toxicogenomics shows promise in using alternative testing methods to predict toxicity before apical endpoints are reached. Gene expression data may have useful applications in regulation of hazardous chemicals and in trauma medicine settings.

# Trainees and Investigators Shine at Fifth Annual Science Day

By Eddy Ball

Now in its fifth year, the NIEHS Annual Science Awards Day is a fall tradition for the Division of Intramural Research. The event celebrates the scientific achievements of investigators and trainees with a full day of oral presentations and poster sessions. This year's event took place November 1 in Rodbell Auditorium and showcased a poster display of 111 abstracts.

Chaired every year since its inception by Special Assistant to the Scientific Director Joel Abramowitz, Ph.D., Science Awards Day features a lecture by the winner of the Scientist of the Year Award and recognition of Mentor of the Year, as well as winning poster, oral presentation, and Paper of the Year achievements by trainees. Thanks to an offer by Library Director Dav Robertson, this year's winning posters remained on display through November in the NIEHS Library.

## 2007 awardees included:

- **Scientist of the Year Award** was presented by Acting Scientific Director Perry Blackshear, M.D., D.Phil., to Laboratory of Signal Transduction Pharmacologist **James Putney, Ph.D.**, who delivered an invited lecture on calcium signaling titled "Calcium Signaling Turned Inside Out." The nomination for Putney by colleague David Armstrong, Ph.D., cited his seminal work authoring the hypothesis that emptying of calcium stores in the endoplasmic reticulum triggers calcium entry across the plasma membrane. Armstrong wrote that Putney's 1986 paper on the hypothesis "has been cited in over 1350 scientific articles... [and] spawned at least three new fields in cell physiology."
- **Mentor of the Year Award** was presented by NIEHS Trainee Assembly Chair Anastasia Wise to Laboratory of Neurobiology Acting Chief **David Armstrong, Ph.D.**, described by one nominator as "an inspiration to many trainees..., [who is] committed to the personal development and career advancement of his trainees and has always been available to them when they wanted to talk with him about both personal and career development advice."



*Following his talk, a relaxed Putney fielded questions from the audience and exchanged banter with colleagues. (Photo courtesy of Steve McCaw)*



*As master of ceremonies, Abramowitz was at the podium off and on throughout the day, introducing speakers, presenting awards and attending to the many details of this special day. (Photo courtesy of Steve McCaw)*

- **Best Poster Presentations** were handed out by Abramowitz:
  - **Environmental Biology** to **Stephanie Nick McElhinny, Ph.D.**, Laboratory of Molecular Genetics, “Strand Assignment of Eukaryotic Replicative DNA Polymerases,” with co-authors Gordenin DA, Stith, CM, Burgers PMJ, Kunkel TA.
  - **Environmental Diseases and Medicine** to **Karina Rodriguez, Ph.D.**, Laboratory of Reproductive and Developmental Toxicology, “Direct Activation of Adenylyl Cyclase Improves the Ovulation Rate of Estrogen Receptor-Beta Null Follicles in Culture,” with co-authors Taniguchi F, Jayes FL, Korach KS.
  - **Environmental Toxicology** to **Dario Ramirez, Ph.D.**, Laboratory of Pharmacology and Chemistry, “A Radical View of Cu, Zn-Superoxide Dismutase-Driven Oxidations: Copper- and Carbonate-Radical Anion-Triggered Protein Radical Chemistry,” with co-authors Gomez-Mejiba SE, Corbett JT, Mason RP.
- **Best Oral Presentation Award** was presented by Abramowitz to **Matthew T. Miller, Ph.D.**, Laboratory of Structural Biology, “Structure of Puf4 Bound to RNA Reveals Insights into Binding Specificity,” with co-author Hall T.

- **Paper of the Year Award** was presented by Blackshear to **Miguel Garcia-Diaz, Ph.D.**, Laboratory of Molecular Genetics, [Garcia-Diaz M](#), [Bebenek K](#), [Krahn JM](#), [Pedersen LC](#), [Kunkel TA](#). 2006. Structural Analysis of Strand Misalignment during DNA Synthesis by a Human DNA Polymerase. Cell 124:331–342.

When he presented the Paper of the Year Award, Blackshear commended Garcia-Diaz for the selection of his paper through rigorous review by the select group of judges from the NIEHS Board of Scientific Counselors. “These studies,” the judges wrote, “contribute significantly to our understanding of basic biology, while disclosing underlying and deleterious processes with implications for environmental health.”

Blackshear also presented an award to Chief of the DNA Replication Fidelity Group Thomas Kunkel, Ph.D., to recognize the lab where Garcia-Diaz and his colleagues performed the experiments that were the basis for the award-winning paper.



*The poster display ran nearly the length of Rall Building. Elaine Gay, Ph.D., center, discussed her work on nicotinic acetylcholine receptors in the Ion Channel Physiology Group with Putney, right. (Photo courtesy of Steve McCaw)*



*Dixie-Ann Sawin, Ph.D., left, explained fine points of her experiments with rafts activation to Toxicologist Alex Merrick, Ph.D. Sawin performed her work as part of the Neurotoxicology Group. (Photo courtesy of Steve McCaw)*



*Environmental Genetics Group fellow Dianne Walters, Ph.D., left, answered questions from Bill Martin, M.D., a pulmonologist and the NIEHS associate director of Translational Research. (Photo courtesy of Steve McCaw)*



*Laboratory of Reproductive Development and Toxicology (LRDT) Chief Ken Korach, Ph.D., right, listened as Yoshihiro Komatsu, Ph.D., outlined his study of developmental disorders in skull formation. Komatsu is a fellow in the Molecular Development Biology group, which is part of LRDT. (Photo courtesy of Steve McCaw)*



*Damien Gawel, Ph.D., right, of the Mechanisms of Mutations Group, offered insights from his study of the role the Dgt enzyme plays in replication errors and mutagenesis to Laboratory of Molecular Genetics colleague Senyene Hunter, Ph.D. (Photo courtesy of Steve McCaw)*



*Blackshear congratulated Kunkel on his lab's contribution to the Paper of the Year. Grateful by the fruits of his labors — and no doubt glad to see the end of a long day — Abramowitz smiled in the background. (Photo courtesy of Steve McCaw)*

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# Melnick Receives 2007 APHA Rall Award

*By Eddy Ball*

National Toxicology Program Toxicologist Ron Melnick, Ph.D., found himself in good company at the November 6 Awards Ceremony held by the American Public Health Association (APHA) during its 135th Annual Meeting in Washington, DC. Melnick was honored at the event for his outstanding contributions to public health with the eighth annual APHA David P. Rall Award for Advocacy in Public Health.

Accepting his award, Melnick stated, “I can think of no greater honor than to be recognized for my efforts applying scientific evidence for the protection of public health. This award is also a very special honor because Dr. Rall, someone I consider to be a giant among public health scientists, hired me into the NTP.” At the awards ceremony, Melnick also expressed his gratitude to Rall for having “the vision and ability to create the world’s premier environmental health sciences research institute.”

Melnick, who has worked at NIEHS since 1980, was nominated by Jennifer Sass, Ph.D., senior scientist at the Natural Resources Defense Council and member of the NIEHS Public Interest Liaison Group. With this award, he joins two former winners also associated with NIEHS, grantee Philip J. Landrigan, M.D., 2003 winner, and NIEHS/NTP Toxicologist James Huff, Ph.D., winner in 2002.

According to the APHA news release, Melnick was honored for his research into the toxicity of such widely used industrial chemicals as butadiene, isoprene, glycol ethers and drinking water disinfection by-products — as well as “for standing up to those who propose weakening chemical exposure standards based on inadequate evidence.”

The association noted his testimony about the chemical DEHP, which is used in the manufacture of several medical devices, and the gasoline additive MTBE. The award committee also recognized his service as an agency representative to the White House Office of Science and Technology Policy and on several scientific review boards and advisory panels, including those of the North Carolina Department of Environment and Natural Resources, the U.S. Environmental Protection Agency and the International Agency for Research on Cancer.

The David P. Rall Award for Advocacy in Public Health is awarded to an individual who has made accomplishments that advanced disease prevention through policy change. The area of consideration for the Rall Award is international in scope, and nominees may include those working in a government agency, academic institution or non-profit organization.

The award was established in memory of Rall, who was NIEHS director for almost 20 years and who created and directed the National Toxicology Program from its inception in 1978 until his retirement from both posts in 1990. The award was created in 2000 to honor the former director, who died following an automobile accident in France the previous September.

The prize is endowed by the Alliance to End Childhood Lead Poisoning and made possible by the contributions of scores of individuals and organizations inspired by Rall’s life work. Melnick described the experience of receiving the award as “invigorating” and said that it gives him added encouragement to pursue his career goals even into retirement.



*Award-winning NIEHS Toxicologist Ron Melnick  
(Photo courtesy of Steve McCaw)*

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# New Editor-In-Chief for *Environmental Health Perspectives*

By Robin Mackar

Hugh A. Tilson, Ph.D. a nationally recognized environmental health scientist, has been named the new editor-in-chief of *Environmental Health Perspectives (EHP)*, a journal published by NIEHS. Tilson will start at NIEHS Nov. 26, 2007 and will officially begin his new role as editor-in-chief January 1, 2008. Since 1972, NIEHS has published *EHP* to provide a worldwide forum for research and education in environmental health sciences.

“Hugh Tilson is an outstanding neurotoxicologist who is well known in the environmental research arena, especially among his former colleagues at NIEHS,” said William J. Martin, M.D., director of the NIEHS Office of Translational Research, which oversees *EHP*. “We are very fortunate to have Hugh with his many years of senior management experience assume this important role.” Tilson worked at NIEHS as a researcher from 1976 to 1989.



Martin, left, helped Tilson with the lapel microphone prior to his open interview at NIEHS on September 13. (Photo courtesy of Steve McCaw)

Tilson was offered the job after undergoing a very competitive, comprehensive and open selection process. The protocol included having a panel of subject matter experts (SME) review all applications received by NIH Human Resources in response to the nationally advertised vacancy announcement. The SME panel helped select the top candidates, who then underwent a series of interviews with *EHP* staff and all NIEHS divisions, including several open forums.

As editor-in-chief, Tilson will be a full-time federal employee responsible for the management of the monthly journal publication, including editorial content, overall operations and supervision of the staff. He will oversee the activities of the Board of Associate Editors and the Editorial Review Board, and he will be responsible for selecting and refilling vacancies on these boards. The boards play a critical role in soliciting and reviewing manuscripts. Tilson will also direct the contract support that assists with the production and distribution of *EHP*.

“I am very pleased to have the opportunity to lead the dedicated staff at *EHP*,” said Tilson. “*EHP* is one of the most important tools we have to get information out to the world about environmental health research. I intend to make it an even more powerful, user-friendly resource.”

Currently, Tilson is serving as the national director for the Human Health Research Program at the Environmental Protection Agency (EPA), a position he has held since 2005. Tilson began working at the EPA in 1989 as director of the Neurotoxicology Division. His tenure at EPA also included five years as the assistant laboratory director for multimedia research in the Research Coordination Branch of the National Health and Environmental Effects Research Laboratory.

Prior to his career at EPA, he served in the Laboratory of Behavioral and Neurological Toxicology and Laboratory of Molecular and Integrative Neuroscience at NIEHS. He has also held various adjunct associate professor positions at UNC Chapel Hill. Tilson received his Ph.D. in psychopharmacology from the University of Minnesota, Minneapolis, and his B.A. in physiological psychology from Texas Technological University in Lubbock, Texas.

Tilson has edited several books and published more than 200 papers in peer-reviewed journals. He has served as the associate editor of science journals, including *NeuroToxicology* from 1978 to 2004 and *Toxicology of Applied Pharmacology* from 1985 to 1995. He has also served on several editorial boards.

Under Tilson's leadership *EHP* will remain an open-access publication, available free of charge [online](#). *EHP* will also continue to be produced as a print journal available through subscription.

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## NIEHS Engages Environmental Health Challenges in Asia

*By Eddy Ball*

Acting Deputy Director Bill Suk, Ph.D., traveled to Bangkok, Thailand for the 6th Princess Chulabhorn International Science Congress (PC VI) November 26 – 29. The conference was his third meeting on the continent this fall as part of NIEHS engagement of environmental health challenges in the developing countries of Asia.

Suk's recent travels to Asia are an integral part of the Institute's pursuit of the fourth goal of the Strategic Plan — to “develop a program in global environmental health.” As he explained in one of the talks he gave in China, “Environmental threats to vulnerable populations in Asia comprise a significant global public health challenge ... [and are certain to grow exponentially] as nations in the region undergo increasingly rapid industrial development.”

At PC VI, Suk chaired a workshop on “Interdisciplinary Approaches to Research on Arsenic Exposure, Susceptibility and Human Health: Current Advances and Future Directions.” The workshop was part of a forum titled “The Interface of Chemistry and Biology in the ‘Omics’ Era” that highlighted how linkages between areas of research growing out of the Human Genome Project can contribute to the treatment and prevention of diseases in the global population. Suk was a part of a group of scientists who shared their expertise on environmental genomics and human health with colleagues from throughout the world.

In October and early November, Suk participated in two back-to-back conferences in Beijing, China. The first was the Pacific Basin Consortium for Environment and Health Sciences 12th International Conference held at Peking University October 26 – 29. There, he delivered a keynote address on “Strategies for Addressing Global Environmental Health Concerns.” The conference was sponsored by eight organizations with interests in global environmental health, including NIEHS, a veteran supporter of the Consortium.

Immediately afterwards, Suk crossed the city to address participants at Forum 11, the 2007 annual meeting of the Global Forum for Health Research October 29 – November 2. As his part of this high-profile gathering, Suk presented a talk on “Promotion of International Collaborative Research Related to Children's Health and the Environment.” Each year at the invitation of the Ministry of Health of the People's Republic of China, the



*According to Suk, international relationship building is the key to maximizing global health resources to address the problem of preventable mortality in developing countries. (Photo courtesy of Steve McCaw)*



meeting brings together several hundred policy makers, researchers and research leaders, and representatives of development agencies, research institutions and the private sector to address gaps in global health research.

This year's forum focused on "Equitable Access: Research Challenges for Health in Developing Countries." The meeting's theme addressed what is known among global health scientists as the "10/90 gap." The term refers to a glaring discrepancy in global health — the imbalance between global health resources, which are less than ten percent of the world's funding for health research, and the magnitude of the problem in developing countries, where more than 90 percent of the world's burden of "preventable mortality" occurs.

In addition to Suk's role in developing partnerships in Asia, efforts to develop a program in global environmental health have included forums held in January and September 2007, co-chaired by William Martin, M.D., NIEHS associate director of Translational Research. During the summer, NIEHS analyzed its grant portfolio as part of an effort spearheaded by Ben Van Houten, Ph.D., chief of the Program Analysis Branch, to maximize current grant opportunities for scientists in developing countries and encourage international partnerships to utilize best the resources available.

Looking to the future, Suk recently announced the appointment of E. Ann Davis, Ph.D., as a special assistant in the Office of the Deputy Director. Davis is on detail from the Fogarty International Center's Division of International Relations, where she was very successful in advancing global environmental health by enabling a broader perspective in building research capacity through creative collaborations. "Ann is the sort of veteran relationship builder who can help NIEHS advance to the next stage of international partnering," Suk said.

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# Science Notebook

## Michael Kastan Gives Falk Memorial Lecture

By Robin Arnette

In Rodbell Auditorium on November 8, Michael B. Kastan, M.D., Ph.D., became the twenty-third scientist to give the NIEHS Hans L. Falk Memorial Lecture, an annual seminar that features a researcher who has made significant contributions to environmental health sciences research. With his talk titled “DNA Damage Response Mechanisms: Implications for Human Disease,” Kastan joined other notable investigators who have received this honor, such as Nobel Laureates Harold E. Varmus, M.D., J. Michael Bishop, M.D., and Sydney Brenner, M.D. NIEHS Acting Deputy Director William Suk, Ph.D., hosted the event.

**Kastan** is the director of the Cancer Center at St. Jude Children’s Research Hospital, but he is best known for his work on the tumor suppressor protein p53. His peer-reviewed journal articles on the involvement of p53 in cellular responses to DNA damage are among the most cited scientific publications of the 1990s. He said that much of that work was funded by NIEHS, and he thanked the institute for that early support. “Dr. Suk put out an RFA [Request for Application] in 1991 that allowed us to ask the question, ‘What controls the progression of the cell cycle in mammalian cells when they’ve been exposed to DNA damaging agents,’” Kastan said. “I’m deeply grateful.”

The crux of that research was based on three pieces of evidence. Kastan and colleagues discovered that after a cell was exposed to ionizing radiation, p53 levels increased. In addition, GADD45, a protein implicated in growth arrest and programmed cell death, was identified as a downstream target of p53. Lastly, they saw that cells taken from patients with the cancer-prone disorder ataxia telangiectasia (AT) failed to induce p53 following ionizing radiation. Kastan said, “We had no idea what gene was missing in these patients, but we knew whatever it was, it signaled the p53.”



*“I’m honored to see my name in the company of these past speakers,” Kastan said at the beginning of his talk. (Photo courtesy of Steve McCaw)*



*Kastan’s talk drew a capacity crowd to Rodbell Auditorium, but the lack of seating didn’t deter Head of the Molecular Development Biology Group Yuji Mishina, Ph.D., right, or Research Fellow Ewa Marczak, Ph.D., from attending the lecture. (Photo courtesy of Steve McCaw)*

Kastan proposed that these data indicated a signal transduction pathway was involved in the response to damage. After publication of the findings, Kastan said thousands of labs around the world studied downstream targets of p53. However, he was more interested in the upstream signaling pathway and knew that the AT gene was involved. After another lab cloned the AT-mutated (ATM) gene in 1995, Kastan finally had the missing piece to the DNA damage signaling puzzle and spent the next decade tracing its molecular steps.

Kastan's concern for cancer patients, though, led him to search for clinical ramifications resulting from studies of DNA damage signaling pathways. Kastan knew that AT patients were more prone to cancers since the mutations in their ATM gene resulted in an inability to activate a critical damage signaling pathway. He postulated that if loss of these pathways could increase cancer development, then perhaps activating such stress response pathways with drugs or other approaches could help prevent cancer or help cells deal with DNA damage. Kastan's lab recently discovered that chloroquine, a commonly used anti-malarial drug, could activate both ATM and p53 at low levels without inducing any DNA damage. He and his colleagues have subsequently discovered that low-dose, intermittent chloroquine treatment could significantly reduce tumor development in mouse models of Burkitt lymphoma and in mice lacking the ATM gene. They are currently working on strategies to optimize this approach as a potential way to reduce cancer development in certain high-risk patient populations.

Kastan ended his seminar by reminding the audience that each human cell experiences up to 10,000 damage events a day, and although the body has repair and other cellular mechanisms to deal with them, biomedical research provides another potential level of intervention. "We've learned enough about these cellular responses that we can begin to intervene for both better treatment of disease and prevention," Kastan said.

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*Host Bill Suk scanned the audience during the question-and-answer session following Kastan's talk. (Photo courtesy of Steve McCaw)*



*Falk's widow, Gabrielle, left, has attended every one of the Falk lectures. Mrs. Falk was joined on the Rall Building patio by her son, Steven, and Kastan. (Photo courtesy of Steve McCaw)*

# GEMS Marks Quarter Century at Annual Fall Meeting

By Eddy Ball

The [Genetics and Environmental Mutagenesis Society \(GEMS\)](#) celebrated 25 years of bringing together the area's junior investigators, trainees and veteran investigators at its 2007 Fall Meeting in Research Triangle Park. Jointly sponsored by NIEHS, the meeting's theme was "Current and Future Issues in Environmental Toxicology."

Gathering at the Radisson Hotel on October 29, more than 100 attendees heard talks on epigenetics, nanotechnology and toxico-cheminformatics interspersed with a poster session, networking lunch and reception, six presented papers and announcements of awards for poster presentations, presented papers and the Presidents Travel Award ([see text box](#)).

Following welcoming remarks by GEMS President Greg Stuart, Ph.D., and President-Elect Rose Anne McGee, NIEHS Acting Director Sam Wilson, M.D., opened the meeting with an overview of the Institute's research "rainbow" and its bearing on the interests of GEMS members, from fundamental work in mechanism-based toxicology to the trans-NIH Roadmap 1.5 Epigenomics Program. "In our portfolio," he observed, "we like to think that there's room for everyone."

Duke University Professor of Radiation Oncology Randy Jirtle, Ph.D., gave the meeting's first keynote talk on "Epigenetics: The New Genetics of Toxicology." An NIEHS grantee, Jirtle has been featured on recent PBS "Nova" programs on epigenetics that explored the fetal origins of adult disease susceptibility in animal models and in humans, including maternal malnutrition and exposures to endocrine disrupting and mimicking compounds.

"Even identical twins that are genetically identical don't necessarily have to have the same epigenome," Jirtle observed. "As a consequence, they can have a variation in disease susceptibilities, behaviors, etc. that are regulated in part by the programming of how the genes are expressed, when and where, rather than changes in mutations."

His talk went on to explore "the glue or the gravity which holds these two time points [fetal exposures and adult disease] together." He discussed the modifications of gene expression effected by DNA methylation and alteration of chromatin structure in response to environmental factors.



*President-Elect McGee, an associate scientific review officer at NIEHS, organized and chaired the 25th anniversary meeting. She will actively promote GEMS membership and usher in the new president-elect, Jeff Ross, Ph.D., of EPA, at the 2008 fall meeting. (Photo courtesy of Steve McCaw)*



*2006-2007 President Stuart observed in his opening remarks that "NIEHS has been a really major benefactor over the years." This is reflected both in the Institute's financial support and in the number of past presidents who have been affiliated with NIEHS. Stuart is a visiting fellow in the NIEHS Mitochondrial DNA Replication Group. (Photo courtesy of Steve McCaw)*

Another emerging concern in relation to long-term health effects of environmental exposures was addressed in a presentation by Andrew Maynard, Ph.D., chief science advisor with the Project on Emerging Nanotechnologies at the Woodrow Wilson International Center for Scholars. Maynard's lecture explored the question, "Nanotechnology: The Next Big Thing, or Much Ado about Nothing?"

Maynard began by underscoring the importance of scale to understanding nanotechnology, which manipulates material that is just above the size of an atom, a scale of one nanometer upwards. The size, he explained, is crucial to both the potential benefits and potential risks of the materials produced. Just as speed can alter the behavior of matter, manipulating the sizes and shapes of materials can give them unique quantum properties.

"We can actually make quite profound changes," Maynard observed, "just by altering the atomic configuration very slightly." These changes can add disproportionate strength and conductivity to materials and expand their dexterity — or enable them to penetrate the tissue barriers between the human organism and the environment to alter dose response.

Ann Richard, Ph.D., gave the final keynote address of the meeting on "Toxico-Cheminformatics: A New Frontier for Predictive Toxicology." Richard is a principal investigator with the U.S. Environmental Protection Agency (EPA) National Center for Computational Toxicology, where she is spearheading the [Distributed Structure-Searchable Toxicity \(DSSTox\) Database Network project](#).

The ambitious DSSTox project endeavors to integrate available and emerging toxicity resources, including the large high-throughput screening (HTS) datasets of the NIH Molecular Libraries Initiative, as well as of toxicity-targeted programs within the EPA, Food and Drug Administration and NIEHS National Toxicology Program. The project uses standardized relational data models to significantly improve public access to information resources.

According to Richard, "Structure annotation of diverse datasets has enabled us to 'look across' these datasets in chemical space, generating chemical overlap matrices to identify those chemicals present in multiple databases of toxicological interest, and to use this information to aid in the selection and prioritization of chemicals for new HTS testing."

## Encouraging the Growth and Development of Young Scientists

A major goal of GEMS is offering students and young scientists an opportunity to learn about areas of current interest with which they may not be very familiar. The meetings also give young investigators an opportunity to network with other scientists and to showcase new research.

Awards to students at the GEMS Fall Meeting included:

- **Best Poster Presentation Awards** (\$250 each category):
  - **Amy McCalla-Martin**, doctoral candidate in the College of Veterinary Medicine at North Carolina State University, for "p19<sup>Arf</sup> Expression in Transient Vasculature Systems of the Developing Mouse," with co-authors Thornton DJ, Mary MN, Skapek SX.
  - **Albert R. Wiegus, Ph.D.**, post-doctoral fellow in the NIEHS Laboratory of Pharmacology and Chemistry Photobiology Workgroup, for "UVA and Visible Light-Induced Cytotoxicity of Fullerol in Human Lens Epithelial Cells," with co-authors Roberts JE, Boyes WK, Andley U, Chignell CF.
- **Best Oral Presentation Award** (\$1,500 stipend for professional development): **Carleitta Paige**, doctoral candidate in the Department of Biochemistry at Wake Forest University, for "The Type III Pantothenate Kinase in *Bacillus anthracis* Is a Likely Candidate for Therapeutic Intervention against Anthrax Infection," with co-authors Reid SD, Hanna P, Claiborne A.
- **25th Anniversary Presidents Travel Award** (\$1,800 contribution by presidents of GEMS to support travel to the Environmental Mutagen Society 2008 Meeting in Puerto Rico):
  - **Dana Dolinoy, Ph.D.**, post-doctoral fellow in the Department of Radiation Oncology at Duke University.
  - **Michele LaMerrill**, curriculum in Toxicology in the Department of Genetics, Center for Environmental and Health Susceptibility at the University of North Carolina at Chapel Hill.



Wilson began his remarks by noting, “Certainly, the title of this society is one that is near and dear to me since my own research interest is in the area of genetic toxicology [and] this area is a major area of interest at NIEHS.” (Photo courtesy of Steve McCaw)



Jirtle was nominated for *Time* magazine’s *Person of the Year* on November 8 by Nora Volkow, M.D., director of the National Institute on Drug Abuse. She praised his work in epigenetics for producing “a far more complete and useful understanding of human development and diseases.” (Photo courtesy of Steve McCaw)



Maynard noted the enormous money-making potential of nanotechnology. According to some predictions, he explained, “By 2014 something like \$2.6 trillion worth of products around the globe are going to be based or dependent in some way on nanotechnology.” (Photo courtesy of Steve McCaw)



According to Richard, a central contribution of the DSSTox project is the development of Standard Chemical Fields, which offer common search metrics to explore diverse toxicity information domains. (Photo courtesy of Steve McCaw)



Oral presentation winner Carleitta Paige pursues her work on anthrax at Wake Forest University on a fellowship from the Department of Homeland Security. Paige entered the competition at the suggestion of her long-distance mentor, NIEHS Director of Education and Biomedical Research Development Marian Johnson-Thompson, Ph.D. (Photo courtesy of Steve McCaw)



The GEMS poster session offered trainees and junior investigators additional opportunities to share their research with colleagues. (Photo courtesy of Steve McCaw)

# Superfund Grantee Shares “Lessons from the Wild”

By Eddy Ball

In his work as director of the Superfund Basic Research Program at Duke University, Toxicologist Richard Di Giulio, Ph.D., combines evolutionary theory, ecology, basic biology and toxicology into a research approach he describes as “evolutionary toxicology.” During his November 2 Frontiers of Environmental Sciences lecture in Rodbell Auditorium, Di Giulio reported on his lab’s investigations into the adaptive phenotype and the resulting fitness costs of a fish species living in a heavily polluted Superfund site on the Elizabeth River in southern Virginia.

Di Giulio’s talk was titled “Environmental Health Lessons from the Wild: Studies of Fish Coping with Pollution” and hosted by NIEHS Associate Director of the Office of Risk Assessment Research Chris Portier, Ph.D. At the beginning of his talk, Di Giulio articulated the motivation for his work in the wild. “What goes on in the outside world can give some interesting insights into the mechanisms of toxicity... [and help] inform what you do in the lab,” he said.

The 47.5-acre site of his research along the Chesapeake Bay tributary is the location of a former wood-treatment facility, Atlantic Wood Industries, Inc. From 1926 to 1991, when the plant ceased operation, its treated-wood storage and waste disposal practices resulted in elevated concentrations of creosote constituents, known as polycyclic aromatic hydrocarbons (PAHs) in sediments adjacent to the site. The PAHs produce a poisonous soup that causes high rates of liver cancer among the fish there.

Di Giulio and his team focused their research on the PAH-resistant Atlantic killifish, which he described as “the darling of adaptation” and “a great lab model” due to its wide distribution, limited home range, and size and behavior. Gene sequencing of the killifish is also well underway, giving the researchers substantial genetic data.

The team used nearby King’s Creek, a pristine tributary of the York River just off the Williamsburg Parkway, as a reference site in their experiments. The researchers bred and interbred fish from both sites to determine the effect of genetics on adaptation to PAHs. They found that resistance to the embryonic anomalies of the cardiovascular system resulting from exposure to sediments was at least partially due to evolutionary



*The killifish does not migrate like other species of fish. “If you see some effect at a particular site,” Di Giulio noted, “you can pretty well bet the bank that those effects emanate from exposures at that site. (Photo courtesy of Steve McCaw)*



*Host Chris Portier, center, and Lockheed-Martin Contractor Nick Straffa, Ph.D., pondered the speaker’s closing observations on the aesthetic and mental health impact of pollution on humans. (Photo courtesy of Steve McCaw)*

adaptation. This resistance carried with it a significant fitness cost — a loss of resilience when exposed as larvae to a very important environmental stressor, oxygen depletion.

“When we started this work,” Di Giulio observed, “we really had no idea what toxicity the Elizabeth River fish were avoiding.” Because single PAH compounds do not produce the congenital deformities observed in King’s Creek fish exposed to the Elizabeth River sediment, the team experimented with several combinations of PAHs to see what if any additive effects a mixture might have. Mixtures containing PAHs that both blocked the CYP1A detoxification enzyme and up-regulated the Aryl Hydrocarbon Receptor-Signaling Pathway produced as much as a three order-of-magnitude increase in toxicity over individual PAHs.

“It’s going to be much more difficult to ferret out this connection in rodent models and so forth,” Di Giulio conceded. Among the “beauties” of working with the killifish, he noted, “is that we can study the heart [of the living killifish] as it develops,” something researchers cannot do as easily with mammals.

In spite of the difficulties involved in establishing biological connections between pollution’s effects on fish and people, Di Giulio remains concerned “that the health of systems pervades into the health of humans in very subtle ways” that do not lend themselves as well to experimentation. Di Giulio closed his lecture as the famous words attributed to Chief Seattle appeared behind him on the final slide of the presentation: “All things are connected. Whatever befalls the earth befalls the children of the earth.”

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## Using Gene Expression for Early Detection of Acetaminophen Overdose

By Robin Mackar

In a new study, researchers report they could detect toxic levels of acetaminophen in laboratory animals by analyzing gene expression in the blood. This NIEHS-funded study could be a first step in developing accurate new tools to detect acetaminophen overdose in humans. Overdose of acetaminophen, the active ingredient in many over-the-counter pain relievers, is a leading cause of liver failure in the United States and is often difficult to diagnose. An estimated 50,000 people seek emergency room treatment for acetaminophen overdose each year.

The research published [online](#) in the *Proceedings of the National Academy of Sciences* shows that gene expression data from blood cells can provide valuable information about acetaminophen levels well before liver damage can be detected by other methods, including serum markers and liver biopsies.



Paules spoke at the December 2006 National Center for Toxicogenomics conference where he presented preliminary findings of microarray detection of acetaminophen overdose in a lecture titled “Linking Phenotype Endpoints with Genomics to Identify Signatures Predictive of Adverse Health Effects.” (Photo courtesy of Steve McCaw)



“In time, this approach could give physicians a powerful new genomics tool to help patients who cannot estimate how much acetaminophen they consumed. Early detection of acetaminophen overdose can be helpful in preventing or treating resulting liver damage,” said Richard S. Paules, Ph.D., principal investigator and director of the Microarray Core Facility at NIEHS and senior author on the new paper.

The researchers would like to build on their findings to develop a simple procedure that clinicians could use in the emergency room to estimate the level of acetaminophen exposure and the potential damage to the liver. This would be especially beneficial for patients such as the elderly, suicidal and semi-comatose who are unable to provide an accurate estimate.

To carry out their study, the researchers developed and then analyzed gene expression signatures, patterns of gene activity, in rats exposed to various doses of acetaminophen. Using microarrays, high-throughput assessment tools that allow scientists to see how differences in gene expression are linked to specific conditions, the researchers were able to determine which genes were turned on or turned off in response to different levels of acetaminophen. Once they selected the gene sets, they tested them for accuracy and found the signature gene lists were able to predict exposure to toxic versus nontoxic doses with very high accuracy (88.9-95.8 percent) — while the more traditional predictors, of clinical chemistry, hematology and pathology were approximately 65 to 80 percent accurate.

“Although it was not the main focus of our study, we wanted to see how applicable this gene expression profiling of blood cells was to humans,” said Raymond W. Tennant, Ph.D., supervisory biologist in the NIEHS Laboratory of Molecular Toxicology, and a co-author on the study.

The NIEHS researchers compared the animal data with data from RNA in blood drawn from individuals who had been admitted to the University of North Carolina emergency room for acetaminophen overdose intoxication. When they compared the toxic blood samples to the samples from normal healthy volunteers, the researchers saw a striking difference.

“Although there are already some good tools available to emergency room physicians to detect liver injury, additional information concerning the level of exposures and/or the degree of liver injury could significantly help us in treating acetaminophen overdose patients,” said Paul Watkins, M.D., director, General Clinical Research Center at the University of North Carolina, Chapel Hill and co-author on the paper.

*Reference:* Bushel PR, Heinloth AN, Li J, Huang L, Chou JW, Boorman GA, Malarkey DE, Houle CD, Ward SW, Wilson RE, Fannin RD, Russo MW, Watkins PB, Tennant RW, and Paules RS. 2007. Blood gene expression signatures predict exposure levels. Proc Natl Acad Sci U S A. DOI 10.1073 PNAS.0706987104 (2007).

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*Tennant was the director of the National Center for Toxicogenomics, which helped pioneer the use of microarray gene expression in predictive toxicology. (Photo courtesy of Steve McCaw)*

# Conference Promotes Bioinformatics in Genomics Fields

By Eddy Ball

NIEHS is helping to open new lines of interdisciplinary communication with its sponsorship of the first in a series of international conferences emphasizing the application of bioinformatics in the fields of toxicogenomics and environmental genomics. The two-day meeting, called the First International Conference on Toxicogenomics Integrated with Environmental Sciences (TIES), was held October 25 and 26 and drew more than 200 scientists to the McKimmon Center at North Carolina State University (NCSU).

The conference featured what NIEHS Bioinformatics Manager and TIES-2007 Organizing Committee member Pierre Bushel, Ph.D., described as “a diverse panel of scientists with a range of expertise, cutting-edge research and technological advances in genomics, toxicogenomics, genetics, proteomics and bioinformatics.” The program also included a student oral presentation competition, poster session and a special session on reports from the FDA-led MicroArray Quality Consortium (MAQC).

Delivering the meeting’s opening remarks, William Slikker, Ph.D., director of the Food and Drug Administration (FDA) National Center for Toxicological Research (NCTR), reflected on the convergence of recent American and European initiatives. “Certainly this [meeting] is one of the first times that all of these kinds of facets are being brought together in an international conference,” he said.

The agenda brought together researchers from the NCTR, several current and former NIEHS grantees, and investigators from universities and institutes across the United States and worldwide. Topics ranged from population gene expression studies that challenge the notion of wild type and strategies for integrating genetics and exposure data, to statistical applications for microarray platforms and the issues of prediction and explanation in biomarker discovery.

NIEHS grantees included keynote speakers Kenneth Ramos, Ph.D., of the University of Louisville, who spoke on genetic regulation of mammalian retroelements, and David Threadgill, Ph.D., of the University of North Carolina (UNC), who addressed the integration of genetics and environmental exposure data.



Conference organizers and student presenters posed for a group photo in the McKimmon Center lobby. Seated, left to right, are NCSU students D. Ryan Georgianna, ClarLynda Williams, and Yunjung Kim. Tuskegee University student Venus Welch sits at the right. Standing, left to right, are Juliebeth Briseno of NCSU, Bushel, Tong and Dahlia Nielsen of NCSU. (Photo courtesy of Steve McCaw)



NIEHS grantee and member of the NIEHS National Advisory Environmental Health Sciences Council Ken Ramos delivered the keynote lecture on the first morning of the conference to a capacity audience at NCSU. (Photo courtesy of Steve McCaw)

Randy Jirtle, Ph.D., of Duke University, delivered the dinner keynote talk on “Epigenetics: The Link between Fetal Exposure and Adult Disease Susceptibility.” Other NIEHS grantees included Ivan Rusyn, Ph.D., of UNC, reporting on liver toxicology, and Daniel Liebler, Ph.D., of Vanderbilt University, exploring protein damage and its consequences.

Four students participated in the student oral presentation competition, with ClarLynda Williams of NCSU winning first place for her work with the Environmental Protection Agency (EPA) [Distributed Structure Searchable Toxicity Database Network \(DSSTox\) Project](#). Placing second through fourth, respectively, were Yunjung Kim of NCSU, Venus Welch of Tuskegee University, a 2007 NIEHS Summers of Discovery intern ([see related Spotlight story](#)), and D. Ryan Georgianna of NCSU.

The special session on MAQC confronted some of the persistent technical issues surrounding the adoption of DNA microarray platforms by the regulatory community. The platform offers researchers and regulators a tool that can evaluate simultaneously the relative expression of thousands of genes, but questions about analytical consistency have long hindered widespread adoption of the methodology.

Currently in Phase II, the MAQC was formed in 2005 to assess the key factors contributing to variability and reproducibility of microarray data among different sites and platforms. The consortium brought together researchers from government, industry and academia to pursue development of a new set of standards and guidelines for the use of DNA microarray data.

The MAQC sessions featured presentations by Weida Tong, Ph.D., director of the Center for Toxicoinformatics at NCTR and technical representatives from several companies involved in microarray applications, including Expression Analysis, Panomics, SAS, Affymetrix, Agilent and Cogenics. The presentations reported on the consortium’s studies of in-lab reproducibility and between-lab reproducibility, correlation of alternative platform results and the overlap of differentially expressed genes among different microarray platforms.

Jointly sponsored by NIEHS, NCSU and NCTR, the conference also received support from JMP Genomics and Rosetta Biosoftware. The meeting set the stage for a second conference scheduled for Spring 2009 at Zhejiang University in HangZhou, China and a meeting planned for 2010 in Germany.



*Also speaking on the morning of the first day of the conference, NIEHS grantee Ivan Rusyn addressed the interface between omics methodologies and toxicology studies in a talk titled “Genetic Genomics and Liver Toxicology: Making New Friends.” (Photo courtesy of Steve McCaw)*



*NIEHS Microarray Core Facility Director Rick Paules, Ph.D., left, and Russ Wolfinger of SAS, who is the leader of the JMP Genomics project and developer of SAS Proc Mixed, served on the TIES program committee and chaired sessions at the conference. (Photo courtesy of Steve McCaw)*



*Not surprisingly, NIEHS Scientific Administrator Jennifer Fostel, left, found plenty to talk about with Tong. The Chemical Effects in Biological Systems (CEBS) database she is instrumental in developing integrates omics data with toxicology, clinical and histopathology data. (Photo courtesy of Steve McCaw)*



*NCSU doctoral student ClarLynda Williams won the \$300 first place award in the student oral presentation. The EPA DSSTox project aims to streamline data mining in the five genomic databases which contain data of chemogenomic interest, including the NIEHS CEBS database. (Photo courtesy of Steve McCaw)*

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## **New ONES Grantees to Visit Institute in January**

*By Robin Mackar*

This year's seven Outstanding New Environmental Sciences (ONES) awardees will visit NIEHS on January 7, 2008 to meet NIEHS staff and make presentations about their work. The ONES awardees will receive five-year grants totaling \$3.5 million to support direct costs, equipment and other resources.

"The ONES program is an important part of our efforts to help establish the careers of creative, talented young scientists and to allow them to apply their talents to the field of environmental health sciences," said Dennis Lang, Ph.D., interim director, NIEHS Division of Extramural Research and Training.

The ONES program, now in its second year of funding, identifies outstanding scientists who are in the early, formative stages of their careers and who intend to make a long term career commitment to research in the mission areas of the NIEHS. The program assists them in launching an innovative research program focusing on problems of environmental exposures and human biology, human pathophysiology and human disease.

"The grantees selected through this very competitive and rigorous review process epitomize the breadth of the NIEHS research program," said J. Patrick Mastin, Ph.D., chief of the NIEHS Cellular, Organ and Systems Pathobiology Branch, which coordinates the ONES program. "These scientists are focusing on conditions such as ADHD, early puberty, aging and lung diseases and determining how these conditions relate to specific environmental exposures. Their research will play a pivotal role in helping to develop new prevention and treatment strategies."

The following is a list of the 2007 ONES program awardees:

- Brent Carter, M.D., University of Iowa, Iowa City, will study the mechanism that causes lung inflammation and fibrosis after exposure to asbestos.
- Wenbin Deng, Ph.D., University of California, Davis, will use a combination of cellular and molecular techniques to study the mechanism which causes lead to be neurotoxic in the developing brain.
- Cheryl L. Fattman, Ph.D., University of Pittsburgh School of Public Health, will conduct studies to help develop new treatments for patients suffering from silicosis. Silicosis, a respiratory disease brought on by inhalation of silica particles, causes chronic inflammation and scarring in the lungs.
- Laura J. Niedernhoffer, M.D., Ph.D., University of Pittsburgh, School of Medicine, will seek to understand the molecular mechanisms by which DNA damage promotes aging. The researcher will examine some common industrial exposures to determine the impact these chemicals have on the aging process and whether they induce DNA damage.
- Timothy R. Nurkiewicz, Ph.D., West Virginia University, Morgantown, will study the mechanisms by which air pollutants, such as particulate matter, cause cardiovascular dysfunction.
- Heather B. Patisaul, Ph.D., North Carolina State University, Raleigh, will study the mechanisms by which common endocrine active compounds, such as bisphenol A and genistein, may impact the endocrine system and potentially advance puberty.
- Jason R. Richardson, Ph.D., University of Medicine and Dentistry of New Jersey, Piscataway, will explore the gene-environment interactions that contribute to attention-deficit hyperactivity disorder (ADHD). The researcher will evaluate pesticide exposure as a potential risk factor for ADHD.

Following the event, the presentations will be made available [online](#). Young investigators interested in competing for funding for next year's program should visit the [ONES \(RO1\) site online](#).

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## Upcoming Distinguished Lecture Features Errol C. Friedberg

*By Eddy Ball*

The 2007-2008 NIEHS Distinguished Lecture Series continues at 11:00 a.m. on December 11 with a talk by Errol C. Friedberg, M.D., titled "Specialized DNA Polymerases in Higher Organisms: Insights from the *Polk* Knock-Out Mouse." Friedberg's talk will take place in Rodbell Auditorium and be hosted by DNA Replication Fidelity Group Chief Thomas Kunkel, Ph.D., and IRTA Fellow Zachary Pursell, Ph.D., of the Laboratory of Molecular Genetics.

Friedberg holds the Senator Betty and Dr. Andy Andujar Distinguished Chairmanship of Pathology at the University of



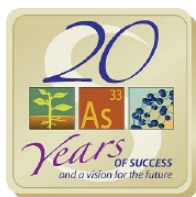
*Distinguished Lecturer Errol Friedberg (Photo courtesy of the University of Texas Southeastern Medical Center in Dallas)*

Texas Southwestern Medical Center at Dallas. He is widely recognized as a leader in the field of DNA damage and repair and as an investigator whose work has contributed to many seminal discoveries in this area of fundamental biomedical research.

By making targeted gene disruptions, Friedberg's lab has developed mouse models for hereditary human diseases. The lab is investigating the predisposition of these mice to various carcinogens, as well as the molecular pathogenesis of cancer in these mouse models. By manipulating expression of translesion DNA polymerases in mice, especially pol kappa (Polk), Friedberg's lab works to increase understanding of the molecular mechanisms by which cells repair and tolerate DNA damage and thereby mitigate against the phenotypic consequences of mutational alterations.

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## Extramural Update



### NIEHS Celebrates the 20th Anniversary of the Superfund Programs

This year marks the 20th Anniversary of the establishment of the two NIEHS Superfund programs, the Superfund Basic Research Program (SBRP) and the Worker Education and Training Program (WETP). NIEHS plans two anniversary celebrations of the programs, which were created under the Superfund Amendments and Reauthorization Act of 1986.

The first Superfund awards were made in 1987.

NIEHS will hold a meeting December 3-5 at Durham's Washington Duke Inn, titled "Superfund Basic Research Program: 20 Years of Success and a Vision for the Future." The Institute will co-host a second event April 3-4, 2008 on the National Institutes of Health campus in Bethesda, Md.

These programs were designed to develop a better understanding of the health effects of hazardous substances, to develop better remediation strategies and to train a work force that can safely clean up hazardous waste spills or respond to emergency spills. Using different, but complementary approaches, the SBRP and WETP have worked to minimize the potential for environmental contamination to impact human health and the environment.

**SBRP:** For 20 years the SBRP has funded basic research that provides a solid foundation of knowledge that can be used by remediators, health professionals and political leaders to make scientifically informed decisions. SBRP-funded researchers have made significant contributions within and across multiple environmental health disciplines:

- Multidisciplinary Research – SBRP was among the first federal programs to require multidisciplinary research that spanned the biomedical and environmental engineering fields. The collaborative efforts have led to significant discoveries about sources of arsenic exposure, impacts of benzene exposure and strategies to reduce exposures to contaminants in drinking water.
- Arsenic – SBRP-funded researchers have made seminal discoveries about the modes of action and pathways of metabolism and detoxification; identified impacts on intellectual development of children; developed analytic methods and screened hundreds of thousands of wells in Bangladesh; and contributed to development of remediation technologies to remove arsenic from drinking water.

- Analytic methods – Before a contaminant can be studied in the human body or in the environment, sensitive and accurate analytic methods are required. SBRP-funded researchers have developed analytic tools to detect and quantify metals, pesticides and organic compounds. They have applied these technologies to design bench and field-applicable methods.
- Remediation – Understanding that prevention of exposure is the best strategy for minimizing the impacts of environmental contamination, the SBRP has funded the development of innovative biological, chemical, physical and nanotechnology methods that effectively remove and/or reduce the amount of hazardous wastes in sediments, soil and other environmental media.

**WETP:** Since its inception, the WETP has funded non-profit organizations to provide occupational safety and health education to target populations of hazardous waste workers and emergency responders. The WETP has provided science-based safety and health training for nearly 2,000,000 such workers. As a cooperating agency named in the National Response Framework’s Worker Safety and Health Support Annex, the WETP can provide high quality site and disaster specific training during national emergencies.

- World Trade Center (WTC) Terrorist Attacks – In response to the attacks, the WETP sent personnel to assist in coordinating WETP grantee activities at the WTC site, assess the safety and health status at the WTC site, evaluate the site safety and health plans, and conduct a preliminary assessment of training needs.
- Hurricanes Katrina and Rita – In the immediate aftermath of Hurricane Katrina, the WETP, its awardees, and the WETP National Clearinghouse for Worker Safety and Health Training developed training materials for response workers; established a field office in Baton Rouge, La.; fielded teams of highly skilled trainers, and conducted safety and health training in English, Spanish and Vietnamese. Nearly 30,000 responders received training because of this effort.
- Avian Influenza – WETP and the U.S. Department of Agriculture Animal and Plant Health Inspection Service (USDA-APHIS) recently sponsored a 3-day conference on protecting Avian Influenza responders attended by nearly 300 industry, labor and government representatives.

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## Extramural Papers of the Month

*By Jerry Phelps*

### Age-Related Cognitive Decline and Lead Exposure

New research by NIEHS-supported investigators suggests that the “normal” cognitive decline experienced as we age may be related to our recent and life-time exposure to lead. In three separate independent epidemiologic studies, bone lead content was associated with poorer measures of cognitive function.

One study included 1,109 former U.S. employees of a tetraethyl lead manufacturing facility. Tetraethyl lead was used in gasoline in the U.S. from the 1920’s to the 1970’s. Another study was based on 803 current and former workers in a Korean inorganic lead industrial setting. Participants in the third study were 1,140 Baltimore residents, aged 50-70, with environmental lead exposure.

Bone lead was measured using X-ray fluorescence of the tibia. The researchers noted a persistent and consistent association of poorer cognitive function with higher tibia lead levels in all three studies. MRI brain scans in the U.S. worker cohort also showed lower brain volumes in people with high tibia lead. The research also indicates that the greater the bone lead content, the sooner the cognitive decline starts.

Added to the knowledge that exposure to lead lowers the peak IQ a person reaches, these studies show that lead exposure is a life-long issue. The authors also point out that the current occupational safety standards for lead workers are inadequate to protect them.

*Citation:* [Stewart WF](#), [Schwartz BS](#). 2007. Effects of lead on the adult brain: a 15-year exploration. *Am J Ind Med* 50(10):729-739.

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## Have Particulate Air Pollution Regulations Affected Mortality Risks?

Particulate air pollution has been linked to cardiovascular mortality and has resulted in increasingly stringent air pollution regulations. Not surprisingly, policy makers and industry officials are eager to know if these tougher regulations are having the desired effect—protecting public health. NIEHS-supported researchers conducted a statistical analysis of particulate matter air pollution and mortality trends from 1987 through 2000, a period during which the EPA set new air quality standards. They found a strong indication that exposures to particulate matter continue to be associated with increased mortality.

Annual averages of ambient air concentrations of particulate matter less than 10 microns and less than 2.5 microns in diameter declined nationwide during the study period. The analysis showed a small decline in the short-term effects of particulate matter on mortality, and most of this decline occurred in counties in the eastern United States.

Called “accountability research,” this type of analysis is relatively new and “is viewed as an emerging component of responsible governmental policy intervention and environmental health tracking and research.” While this study does not provide conclusive evidence of health benefits from more stringent regulation, it does have the potential to provide necessary data for regulatory agencies so that informed decisions can be made.

*Citation:* [Dominici F](#), [Peng RD](#), [Zeger SL](#), [White RH](#), [Samet JM](#). Particulate air pollution and mortality in the United States: did the risks change from 1987 to 2000? *Am J Epidemiol*. 2007 Oct 15;166(8):880-8.

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## Statin Drugs Maintain Lung Function in the Elderly

Cholesterol-lowering statin drugs have become increasingly popular since their introduction in the 1990’s, with about 12 million current prescriptions in the U.S. for patients with cardiovascular disease risk. Statins have also been shown to have anti-inflammatory and anti-oxidant properties. NIEHS-supported investigators hypothesized that the drugs may have a beneficial effect on maintaining lung function in elderly subjects by reducing inflammation and oxidative stress.



The researchers performed their study with a population of men, average age greater than 70, enrolled in the Normative Aging Study. Lung function tests had been performed on these men 2-4 times between 1995 and 2005. At each visit, the subjects were questioned about their use of statins as well as their smoking history. In summary, statin use reduced the yearly decline in “normal” lung function by about 50 per cent. Statin use significantly reduced the deficits in both forced expiratory volume and forced vital capacity in smokers and non-smokers.

This study is the first to show the benefits of statin use for maintaining lung function in elderly subjects regardless of smoking history. If confirmed in a randomized clinical trial, these results point to a possible treatment for impaired lung function, especially in patients with a history of smoking.

*Citation:* Alexeeff SE, Litonjua AA, Sparrow D, Vokonas PS, Schwartz J. 2007. Statin use reduces decline in lung function: VA Normative Aging Study. *Am J Respir Crit Care Med* 176(8):742-747.

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## **Polymorphisms in Nucleotide Excision Repair Genes and Breast Cancer Risk**

Genes responsible for nucleotide excision repair, the process that removes bulky DNA adducts, are thought to be cancer susceptibility genes. In a collaborative study, NIEHS grantees at the Columbia University Mailman School of Public Health and the University of North Carolina School of Public Health investigated whether single nucleotide polymorphisms of nucleotide excision repair genes are associated with changes in the risk for breast cancer.

The researchers analyzed a population-based breast cancer case-control study on Long Island, New York. They examined polymorphisms in four nucleotide excision repair genes in over one thousand breast cancer cases and a similar number of control subjects. Study subjects with at least one variant allele in the gene *XPB* were found to have a 25 per cent greater risk for breast cancer. The risk was almost two times as high in subjects with detectable DNA adducts. Although the increases in risk are modest, they were statistically significant.

In summary, this study suggests that certain polymorphisms in nucleotide excision repair genes increase the risk of breast cancer in women. The risk is increased when DNA adducts are present. These results may improve the identification of high-risk individuals and preventable environmental risk factors for breast cancer.

*Citation:* Crew KD, Gammon MD, Terry MB, Zhang FF, Zablotska LB, Agrawal M, Shen J, Long CM, Eng SM, Sagiv SK, Teitelbaum SL, Neugut AI, Santella RM. 2007. Polymorphisms in nucleotide excision repair genes, polycyclic aromatic hydrocarbon-DNA adducts, and breast cancer risk. *Cancer Epidemiol Biomarkers Prev* 16(10):2033-2041.

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# Intramural Papers of the Month

By Robin Arnette

## Identification of a New Base Excision Repair Cofactor

An international team of researchers jointly funded by NIEHS and the Japanese government have reported that high-mobility group box 1 (HMGB1)—a nuclear non-histone chromosomal protein that transiently introduces bends into linear DNA—is a cofactor involved in mammalian base excision repair (BER).

When cells are exposed to genotoxic chemicals such as methylating agents, deoxyribose phosphate (dRP) often appears as a cytotoxic lesion at the 5' side of a DNA gap (5'-dRP). Removal of the 5'-dRP BER intermediate, primarily performed by Pol  $\beta$ , allows proper BER function to continue. However, when this Pol  $\beta$  activity is deficient, other BER cofactors must be able to remove the 5'-dRP. To determine which mammalian proteins are capable of interacting with 5'-dRP BER intermediates and removing the 5'-dRP group, the team performed experiments with a Pol  $\beta$  null mouse embryonic fibroblast cell extract. A protein and DNA complex capable of forming a Schiff base with the 5'-dRP intermediate was isolated and then the protein in the complex was identified by mass spectrometry analysis.

The analysis revealed that HMGB1 was the major BER intermediate interactive protein in the extract. Subsequent experiments using photoaffinity labeling, DNA/protein-binding assays, enzymatic assays, and immunofluorescence with GFP-tagged HMGB1 determined that HMGB1 in the cell both stimulates base excision repair and interacts with BER-related enzymes. HMGB1 appears to serve as a platform upon which the enzymatic transactions of DNA repair occur more efficiently.

This report is the first to identify the chromosomal protein HMGB1 as a base excision repair accessory factor.

*Citation:* Prasad R, Liu Y, Deterding LJ, Poltoratsky VP, Kedar PS, Horton JK, Kanno SI, Asagoshi K, Hou EW, Khodyreva SN, Lavrik OI, Tomer KB, Yasui A, Wilson SH. 2007. HMGB1 is a cofactor in mammalian base excision repair. *Mol Cell*. 27(5):829-841.

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## A Novel Mechanism for Integrating Inositol Phosphate Signaling Pathways

Scientists from NIEHS, Novartis Research Foundation and Virginia Tech have published a report in the *Journal of Biological Chemistry* demonstrating that a human inositol phosphate kinase (hITPK1) catalyzes phosphate exchange between two inositol phosphates from separate metabolic branches of this cell-signaling family. NIEHS and the U.S. Department of Energy funded the study.

Inositol 1,3,4 trisphosphate [Ins(1,3,4)P<sub>3</sub>] is a by-product of a signaling cascade that elevates cytoplasmic calcium. [Ca<sup>2+</sup>]. Ins(1,3,4)P<sub>3</sub> exists in a metabolic pathway that is separate from inositol 1,3,4,5,6 pentakisphosphate [Ins(1,3,4,5,6)P<sub>5</sub>], which ITPK1 dephosphorylates to inositol 3,4,5,6-tetrakisphosphate [Ins(3,4,5,6)P<sub>4</sub>], an inhibitor of plasma membrane chloride channels. This study shows that hITPK1 functionally

interconnects these two signaling pathways via an unprecedented “intersubstrate phosphate transfer” reaction:  $\text{Ins}(1,3,4)\text{P}_3$  accepts the 1-phosphate from  $\text{Ins}(1,3,4,5,6)\text{P}_5$ , yielding  $\text{Ins}(3,4,5,6)\text{P}_4$ . ITPK1 homologues from soybean and *Entamoeba histolytica* are not active phosphotranferases. To explain why the homologues are not active, the authors obtained structural data by crystallographic analysis, and then performed site-directed mutagenesis. They concluded that phosphotransferase activity requires amino-acid residues in the hITPK1 active site that are absent in plant and protozoan homologues.

These studies show how the catalytic activity of hITPK1 impacts regulation of diverse mammalian cellular functions such as fluid secretion, insulin secretion and neurotransmission.

*Citation:* Chamberlain PP, Qian X, Stiles AR, Cho J, Jones DH, Lesley SA, Grabau EA, Shears SB, Spraggon G. 2007. Integration of inositol phosphate signaling pathways via human ITPK1 J Biol Chem. 282(38):28117-28125.

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## Hydrophobicity is Necessary in nAChR Signaling

In a study funded by the NIH Intramural Research Program and published in the October issue of *Molecular Pharmacology*, NIEHS investigators from the Laboratory of Neurobiology and the Scientific Computing Laboratory reported that hydrophobic interactions are essential for apolipoprotein E (apoE) inhibition of acetylcholine responses mediated by the neuronal nicotinic acetylcholine receptor (nAChR). Drugs that act on nAChRs are promising therapeutic targets for many neurological disorders such as Alzheimer’s disease, Parkinson’s disease, epilepsy and schizophrenia.

Previous studies had determined that peptides derived from apoE inhibited native and recombinant homomeric alpha-7 subunits ( $\alpha 7$ ) of nAChRs in *Xenopus laevis* oocytes, but the team wanted to study the specific interaction responsible for channel inhibition. The researchers used binding studies, site-directed mutagenesis of  $\alpha 7$  nAChRs and mutated apoE peptides to characterize the binding interaction. They created multiple  $\alpha 7$  nAChR mutants including a tryptophan to alanine mutant ( $\alpha 7$ -W55A), and also mutated apoE<sub>141-148</sub> — the peptide that inhibited nAChR function—by substituting two positively charged lysines with leucines (apoE<sub>141-148</sub>2K/2L) or glutamic acid (apoE<sub>141-148</sub>2K/2E).

In assays, the  $\alpha 7$ -W55A mutant demonstrated diminished inhibition by apoE peptides of the acetylcholine-activated  $\alpha 7$  nAChR. Computer modeling of apoE peptide docking to the  $\alpha 7$  nAChR confirmed the functional data. The hydrophobic interactions generated between apoE<sub>141-148</sub> and the  $\alpha 7$  nAChR interface are necessary for peptide inhibition of nAChR signaling.

*Citation:* Gay EA, Bienstock RJ, Lamb PW, Yakel JL. 2007. Structural determinates for apolipoprotein E-derived peptide interaction with the alpha 7 nicotinic acetylcholine receptor. Mol Pharmacol. 72(4):838-849.

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# The Role of Accessory Proteins in Translesion DNA Synthesis

In a study published in the journal *Biochemistry*, researchers from NIEHS and Washington University School of Medicine in St. Louis reported on the effects of replication accessory proteins on translesion synthesis (TLS) by DNA polymerase eta (pol eta) in the budding yeast *Saccharomyces cerevisiae*. The study was funded by the NIEHS Intramural Research Program and the NIH.

TLS allows organisms to bypass lesions that block DNA synthesis by replicative polymerases. Human and yeast cells lacking pol eta display increased mutagenesis following ultraviolet light (UV) exposure, indicating that pol eta suppresses mutagenesis caused by UV-induced DNA damage, and humans lacking pol eta are highly susceptible to skin cancer. Pol eta is known to perform low-fidelity bypass of the UV light induced *cis-syn* thymine-thymine dimer (TT dimer), and the team asked whether other proteins could improve the efficiency and/or the accuracy of this bypass.

The investigators measured the efficiency and fidelity of TT dimer bypass by pol eta in the absence or presence of proteins involved in DNA replication: RPA (single stranded DNA binding protein), PCNA (the eukaryotic sliding clamp) and RFC (the clamp loader complex). The results demonstrated that these three accessory proteins have at most subtle effects on TLS efficiency and fidelity, indicating that the pol eta itself plays a dominant role in the TLS-dependent suppression of UV light-induced mutagenesis and carcinogenesis in humans.

*Citation:* [McCulloch SD, Wood A, Garg P, Burgers PMJ, Kunkel TA](#). 2007. Effects of accessory proteins on the bypass of a *cis-syn* thymine-thymine dimer by *Saccharomyces cerevisiae* DNA polymerase eta. *Biochemistry*. 46(30):8888-8896.

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# Inside the Institute

## Employees Mix and Mingle at Nottingham

*By Eddy Ball*

It didn't take long for most people at the Institute's first Mix and Mingle session in Nottingham Hall November 14 to see the wisdom behind the new series of get-togethers initiated by NIEHS Acting Director Sam Wilson, M.D. Once the event was underway, Nottingham staff and their visitors alike seemed to agree about the desirability of getting together more often in the future.

When he arrived at the gathering, Wilson humbly admitted that he had followed Associate Director of Management Marc Hollander's motorcycle over to the satellite office space because he thought he might get lost. "The last time I tried to drive to Nottingham," he joked, "I ended up at the airport."

The group of nearly fifty employees and contractors had a chance to chat with Wilson and, in some cases, put faces to several names they may have heard many times before — as well as meet some people they didn't know even existed.

Along with Wilson, the Nottingham visitors included four suited-out associate directors, Acting Director of DERT Dennis Lang, Ph.D., Acting Scientific Director Perry Blackshear, M.D., D.Phil., and B-module heavy lifters Lindsay Lloyd and Angie Sanders. Although some of the people who call Nottingham home knew all of the visitors, almost no one had yet met the newest NIEHS associate director, Sharon Hrynkow, Ph.D., who spends most of her time in Bethesda.

Refreshments were simple, but popular among the mix-and-mingle crowd, and the success of the event was evident from the paucity of leftovers in the Nottingham break room the next morning.

The series continues in December with Mix and Mingle sessions slated for East Campus and Main Campus.



*The event gave Nottingham staff, such as John Peterson of OCPL, second from left, and Nancy Stegman, second from right, a chance to chat with Associate Directors Chris Portier, Ph.D., left, Allen Dearry, Ph.D., right, and Wilson, center. (Photo by Eddy Ball)*



*With many of his staff located at Nottingham, Hollander was a familiar face. (Photo by Eddy Ball)*



*Before the visitors arrived, some Nottingham regulars spent a little time mixing and mingling on their own. Shown left to right, Dona McNeil, second from left, Nancy Powell and Ellen Moul listened as Kelly Powel, left, gestured as she made a point. (Photo by Eddy Ball)*



*Lang, left, chatted with OCPL News Director Robin Mackar about his upcoming trip to Ireland, where, he noted, “my Blackberry won’t work.” (Photo by Eddy Ball)*

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## Cherokee Historian Gives Heritage Month Talk at NIEHS

*By Eddy Ball*

Eastern Band of the Cherokee historian and Welcome Center representative Buck West shared his personal and tribal history with NIEHS staff during a Native American Heritage Month lecture November 14. The event was sponsored by the NIEHS Diversity Council and hosted by Staff Scientist Angela King-Herbert, D.V.M.

West, who is a sixth generation descendent of one of the Eastern Band’s most important leaders, captivated the audience gathered in Rodbell Auditorium with a narrative of his people’s tragic and resilient history from the 1500s, when the Cherokee first encountered Europeans, to the present, as they experience a kind of political and cultural renaissance.

Along with the history of his people, West also shared important events from his own life. He was visibly moved as he recalled the humiliation and loss of cultural heritage experienced by generations of Cherokee children in missionary and federally controlled schools. “As a school boy in the 1950s,” he explained, “I was whipped for speaking the language of my people.”



*Shown here at the NIEHS Travel Show in April, West found himself at the other end of Rodbell before an audience, giving a talk on the history of his tribe. (Photo by Eddy Ball)*

In many respects, West’s story was a chronicle of loss — a sovereign land appropriated by government decree despite a Supreme Court decision in the tribe’s favor and an advanced culture oppressed by American settlers hungry for gold in the mountains of north Georgia and Western North Carolina. The commandeering of their lands sent the Cherokee on a disastrous forced march to Oklahoma, a journey known as the “Trail of Tears” that killed between one-quarter and one-third of their 1838 population of 17,000 people. The oppression of their culture wreaked spiritual malaise among the Cherokee, nearly wiping out their time-honored customs, heritage and language.

However, West, his daughter, who now teaches the Cherokee language, and his illustrious ancestor, Chief Yonagusta, are examples of how the Cherokee people worked patiently over the years to make the future better. West and his daughter are part of the contemporary movement to preserve Cherokee history and the tribe’s language, the sole Native American language with its own orthography. Without Yonagusta, there might very well not be an Eastern Band of the Cherokee Indian as it now exists.

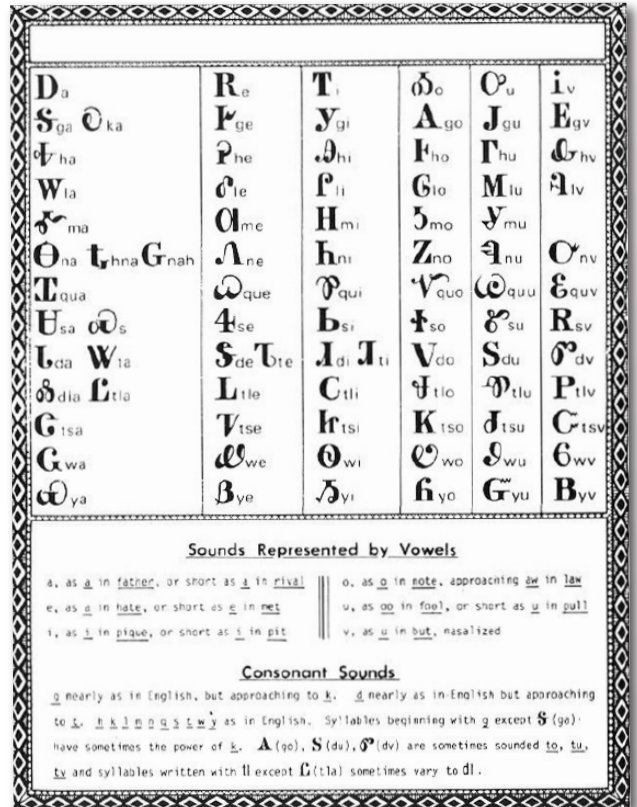
The Cherokee language has a phonetic syllabary invented in the 1820s by Sequoyah, the only individual in recorded history to single-handedly develop a system of writing for a spoken language. The tribe started its own newspaper, the *Cherokee Phoenix* in 1828, created a written constitution and laws, and translated the Bible into Cherokee. “We were the first people ‘hooked on phonics,’” West joked as he catalogued the tribe’s accomplishments, including almost universal literacy by the mid 1830s — something most of their white neighbors were too illiterate to appreciate.

According to West, Yonagusta, the chief who stayed behind to lead the thousand or so tribal resisters of the forced relocation, convinced the tribe with a deathbed request in 1839 to accept his adopted son, the white trader Will Thomas, as their next chief. The Cherokee were not considered citizens of North Carolina at the time, but Thomas, by virtue of his racial identity, could buy and own land. Using his own money and the money of his people, Thomas helped the tribe acquire the 56,000 acre tract adjacent to the Great Smoky Mountains National Park now known as the Qualla Boundary.

Today, a revitalized Eastern Band governs its six townships and the education of its children, who are required to study Cherokee language and history in order to graduate from high school. Tourism and gaming provide additional revenue for the isolated communities of the Qualla Boundary.

The tribe and the Cherokee Historical Association have helped revive the Eastern Band’s history and culture with the Museum of the Cherokee Indian, the Oconaluftee Indian Village, where West also works as an historical interpreter, the Qualla Arts and Crafts Mutual and the Cherokee Cultural Resources Office. Nearby county high schools, Western Carolina University and Southwestern Community College also support Cherokee heritage with courses in the tribe’s language and history.

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*The Cherokee syllabary is a set of 86 symbols combining Roman type, curls and dashes. Each distinct letter stands for a syllable in the Cherokee language. (Graphic courtesy of the Sequoyah Birthplace Museum in Vonore, Tennessee)*

# O'Fallon Competes in World Championship

*By Eddy Ball*

People who think that even world-class athletes need a break after a tough competition haven't yet talked to NIEHS Program Administrator Liam O'Fallon. On October 21, only three weeks after competing at the National Long Course Duathlon Championships on the grueling Powerman Ohio course in Mansfield, Ohio, Liam found himself at the starting line of the Long Course Duathlon World Championship in Richmond, Va.

As he completed nearly four hours of running 15 kilometers, cycling 76 km. and running again 7.5 km. through downtown Richmond in the first Long Course Duathlon World Championship held in the US, the athlete's thoughts were not on cool beverages and much needed rest — but on the next challenge he plans to take on and how to convince his family that he hasn't lost his mind.

O'Fallon finished 16th in his 35 to 39 age group with a time of 3:53:22, putting in a better performance than two of the professional athletes in the Elite Men's competition. However, almost as soon as he crossed the finish line, he recalled, "I was left with a gnawing feeling down deep that I can do better, much better." He said that he was exhausted and felt like throwing up, but he was already thinking about how he could train better for the event next year in Vancouver, B.C. or in the Short Course World Duathlon in Rimini, Italy in 2008

At NIEHS, O'Fallon is known as a sure bet in any race he enters. In fact, it was a Combined Federal Campaign fundraising run-bike competition between the US EPA and NIEHS that sparked Liam's interest in and passion for duathlons. He recalls finishing the race with such euphoria that he immediately began training for Powerman North Carolina. He is a veteran competitor who comes to his athletic trials armed with nutritional supplements, energy drinks, self-psyching mantras and the experience to anticipate problems he could face from dehydration, nausea and fatigue.

The duathlon is an athletic event involving two types of competition, running and cycling, rather than three, as in the better-known triathlon, which also includes swimming. Duathletes run, then bike and then run again. Governed by the same group, the International Triathlon Union, duathlons are just as demanding and their athletes are just as fiercely loyal and enthusiastic. However, because the triathlon has achieved Olympics recognition, duathlon is much less a part of the American vocabulary — and very often confused with "biathlon," a term purists reserve for describing the Winter Olympics competition featuring skiing and marksmanship.

Training for such an event requires a considerable amount of time. To minimize the impact on his family, O'Fallon can be found training for his events in the wee hours of the morning with a couple of his fellow NIEHS co-workers who challenge him to excel. He also finds that teaching indoor cycling Spinning classes twice a week at 5:45 a.m. helps prepare him for the cycling portion of the race. The competition in Richmond was his first world championship try, but if his finish there is any indication, it won't be his last. O'Fallon is not the kind of athlete to be satisfied with turning in anything but the best performance he is capable of giving.

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*Competing in a duathlon involves alternately running and cycling at full speed. (Photo courtesy of Steve McCaw)*



*O'Fallon puts everything he has into the final stretch of an event held on the NIEHS campus. (Photo courtesy of Steve McCaw)*



*His fellow runners and cyclists are used to seeing O'Fallon finish at the top in local and regional races. (Photo courtesy of Steve McCaw)*





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