



NIEHS Spotlight



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Leaders Discuss University of New Mexico Research

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Science Notebook



The Role of MAPK Pathways in Metastasis

The mitogen-activated protein kinase (MAPK) pathways are signal transduction cascades that regulate gene expression, cell growth and development, and apoptosis or cell death. ...[read more](#)



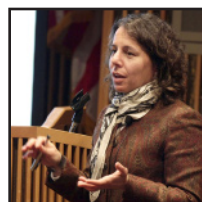
Columbia University Researcher Discusses Mitochondrial Disorders

On January 13, Salvatore DiMauro, M.D., a leading researcher in the study of mitochondrial disorders, gave a distinguished lecture at NIEHS titled "Mitochondrial Medicine." ...[read more](#)



Study Offers Insight into Endocrine Disruption by Soy

NIEHS-supported researchers report compelling new evidence about the mechanisms linking genistein supplementation during development of mice to altered DNA methylation patterns that can lead to serious health complications later in life, according to a study published in the journal *Endocrinology*.[read more](#)



Trainees Host Stress-Induced Mutagenesis Seminar

On January 5, the NIEHS welcomed Susan Rosenberg, Ph.D., a professor at the Baylor College of Medicine, who conducted a thought-provoking seminar regarding DNA mutation in response to environmental stress.[read more](#)

NIEHS Spotlight



Robertson Chairs SLA Centennial Commission

NIEHS Library Director Dav Robertson is excited about the 100th anniversary of the Special Libraries Association (SLA) and his appointment as chair of the 2009 Centennial Commission. ...[read more](#)



Distinguished Guest Gives Disability Presentation

On January 13, the NIEHS Diversity Council Disability Advocacy Committee (DAC) welcomed as its keynote speaker one of the highest ranking officials with a disability in the federal government today, Special Assistant to the Assistant Attorney General for Civil Rights in the Department of Justice (DOJ) Ollie Cantos, J.D.[read more](#)



Superfund Grantees Begin Work on Documentary Series

With support from the NIEHS Superfund Basic Research Program (SBRP), researchers at the University of California, San Diego (UCSD) are following a road less traveled in order to translate their scientific research into policy and public health information. ...[read more](#)

UC Davis Study Examines Rise in Autism Rates

A new analysis of data on autism performed by NIEHS grantees at the University of California Davis (UCD) undermines arguments that California's dramatic 7- to 8-fold increase in autism cases may be largely due to changing diagnostic practices of physicians.[read more](#)



Former Postdoc Joins Biotech Management Team

In December 2008, Cellular Dynamics International (CDI) of Madison, Wis. announced the appointment of three new executives, including former NIEHS Postdoctoral Fellow Emile Nuwaysir, Ph.D., to lead the company as it attempts to industrialize stem cell technologies after raising \$18 million in venture capital.[read more](#)

Science Notebook



Nano Research Pioneer Speaks at NIEHS

Duke University nanomaterials specialist Mark R. Wiesner, Ph.D., made his first visit to NIEHS on January 9 as a guest lecturer in the Frontiers of Environmental Sciences series. His talk, "Reducing Uncertainty Surrounding Environmental Risks of Nanomaterials: Assessing Transport and Transformation," kicked off the 2009 series...
...[read more](#)



Upcoming Distinguished Lecture Features Michael Mendelsohn

NIEHS will welcome the next speaker in its 2008-2009 Distinguished Lecture Series on February 10 at 11:00 a.m. in Rodbell Auditorium. Michael Mendelsohn, M.D., will present a seminar on "Estrogen Receptor Action in the Cardiovascular System" hosted by NIEHS Principal Investigator and Chief of the Receptor Biology Group Ken Korach, Ph.D. ...[read more](#)



Cidlowski to Speak in Duke Immunology Seminar Series

NIEHS Principal Investigator John Cidlowski, Ph.D., will lecture on February 17 at 4:00 p.m. in 143 Jones Building on the Duke University campus. His talk, "The Secret Lives of Glucocorticoid Receptors," is part of the Duke University Medical Center Department of Immunology Seminar Series. ...[read more](#)



This Month in EHP

The February 2009 issue of Environmental Health Perspectives is now available on-line, highlighting issues surrounding global warming/ climate change, endocrine disruptors and the health effects of air pollution. ...[read more](#)

Inside the Institute



Wilson to Focus on Research Full Time

Samuel H. Wilson, M.D., the long-time Deputy Director and recent Acting Director of the National Institute of Environmental Health

Sciences (NIEHS) and the National Toxicology Program (NTP), announced his decision to step away from his administrative roles at the Institute. ...[read more](#)



NIEHS Scientists Get Tips on Giving Better Presentations

Developing and delivering a compelling PowerPoint presentation can be a challenge, but for the 24 scientists who participated in a two-

day training class coordinated by the NIEHS Office of Communications and Public Liaison (OCPL), that task may now be a little easier. ...[read more](#)



NIEHS Staffers Bring Help to Durham Homeless

The bitter cold on Friday January 16 failed to hamper the generosity of a group of NIEHS employees who transported donated food to a shelter

for the homeless in Durham, NC.[read more](#)

Extramural Research

Extramural Update

After fifteen months of work dedicated to the establishing the new Partnerships for Environmental Public Health (PEPH) program, the Division of Extramural Research and Training (DERT) at NIEHS announced the first Request for Applications (RFA) titled “Research to Action: Assessing and Addressing Community Exposures to Environmental Contaminants.” ...[read more](#)

Extramural Papers of the Month

- [Selenium May Prevent High-Risk Bladder Cancer](#)
- [Gene Packaging is Important in Cancer](#)
- [Dopamine Transmission Impaired by Manganese](#)
- [Dioxin Disrupts Prostate Development](#)

Intramural Research

Intramural Papers of the Month

- [Researchers Find a Novel Target for Glycogen Synthase Kinase 3Beta Phosphorylation](#)
- [The Histone Deacetylase Inhibitor Trichostatin A Upregulates NAG-1](#)
- [A Role for CYP2J5 in Blood Pressure Regulation via an Estrogen-Dependent Mechanism](#)
- [Computational Studies of the Catalytic Mechanism of Human DNA Polymerase Lambda](#)

Calendar of Upcoming Events

- **February 5 (offsite event)**, 103 Bryan Research Building at Duke University, 12:00 – 1:00 — Ion Channel Research Unit Seminar Series with ONES grantee Sven-Eric Jordt Ph.D., speaking on “Sensory TRP Channels in Airway Reflex Control and Inflammation”
- **February 5 – 6 (offsite event)**, Turin, Italy — Lorenzo Tomatis Conference on Environment and Cancer
- **February 6 (offsite event)**, at the University of North Carolina at Chapel Hill Blue Cross & Blue Shield of North Carolina Foundation Auditorium, 8:30 – 11:30 — The Molecular Epidemiology of Cancer: Perspectives and Approaches, A Symposium in Honor of Dr. Barbara Sorenson Hulka, [registration required](#)
- **February 10**, in Rodbell Auditorium, 11:00 – 12:00 — NIEHS Distinguished Lecture Series featuring a talk on “Estrogen Receptor Action in the Cardiovascular System” by Mike Mendelsohn, M.D.
- **February 11 – 13 (offsite event)**, at Columbia University — “Translating Superfund Basic Research Program Triumphs into Public Health Progress: Understanding and Implementing Effective Research Translation”
- **February 13**, in Rodbell Auditorium, 9:00 – 10:00 — Frontiers of Environmental Sciences Lecture Series
- **February 17 (offsite event)**, 143 Jones Building at Duke University, 4:00 – 5:00 — Duke Department of Immunology Seminar Series featuring John Cidlowski, Ph.D., addressing “The Secret Lives of Glucocorticoid Receptors”
- **February 18**, in Rall D-350, 11:00 – 12:00 — Seminar on “Disclosing Conflicts of Interest in Clinical Research: Attitudes of Investigators, IRB Members, and Research Subjects,” featuring Kevin Weinfurt, Ph.D.
- **February 19**, in Rodbell Auditorium, 8:30 – 5:00 — National Advisory Environmental Health Sciences Council (NAEHSC) meeting
- **February 20 (offsite event)**, Searle Conference Center at Duke University, 8:30 – 5:00 — Managing Toxic Risks for Global Health Symposium, presented by: Integrated Toxicology and Environmental Health Program, Superfund Basic Research Center and the Duke Global Health Institute, [registration required](#)
- **February 24**, in Rodbell Auditorium, 8:30 – 5:00 — NTP Board of Scientific Counselors Meeting
- **February 25**, in Rodbell Auditorium, 8:30 – 5:00 — NTP BSC Technical Reports Review Subcommittee Meeting
- **February 26**, in Rodbell Auditorium, time TBA — Multi-Cultural Event
- View More Events: [NIEHS Public Calendar](#)

NIEHS Spotlight

Birnbaum Greets Employees at Town Hall

By Eddy Ball

Speaking to a standing-room-only audience on January 26, new NIEHS Director Linda Birnbaum, Ph.D., offered employees a preview of what they can expect from her leadership during an hour-long talk and question-and-answer session. Her tone was upbeat and often humorous, and her audience greeted her remarks on several occasions with applause during this important moment in the history of NIEHS.

During her talk, she pointed to initiatives she has already put in place, such as the anonymous director's suggestion box now available on the NIEHS internal Junction website, and her plans to improve the organizational climate at the Institute. She pleased many of listeners by announcing that she would not set up her own lab in the near future, but instead focus her complete attention on the operation of the Institute.

Describing NIEHS as the “premier environmental health organization in the world,” Birnbaum introduced her themes early in the talk. “NIEHS has been through a rough time,” she conceded, but emphasized that “we can do better” and emerge “a more cohesive group” than before — restoring trust in leadership and mending fences within NIEHS and with NIH, other federal agencies and the Institute's constituencies. She said she plans to make no major personnel changes until she has had a chance to understand better the needs of the Institute.

To that end, Birnbaum has opened communication with the NIEHS Assembly of Scientists and the NIEHS Trainees Assembly. She has adopted an open-door policy and invited employees to feel free to call and write her with suggestions or to stop her in the hallway to talk.

Birnbaum said that she plans to invite a number of directors of other NIH ICs and high-level management personnel to visit NIEHS as guest speakers and that she plans cooperative efforts for shared resources with the Environmental Protection Agency and other federal agencies. She also plans to continue the leadership's outreach and support efforts for grantees and other constituencies.



Birnbaum was at ease with the audience from the outset. Several people in the audience had been colleagues when she worked at NIEHS 19 years ago, while others she knows from collaborations and meetings. (Photo courtesy of Steve McCaw)



The crowd, including Biologist Marilyn Ehrenshaft, Ph.D., left, and Chemist Jean Corbett, lined the walls of Rodbell Auditorium. Some employees stood outside in the hall and lobby as they listened. (Photo courtesy of Steve McCaw)

With a fresh and engaging humility that gave added force and credence to her words, Birnbaum focused on the qualities that she values in an organization — open minds, respect for colleagues, divergent thinking, diversity, full disclosure, fairness, responsibility, accountability and a constructive, open environment that leads to genuine two-way communication.

Birnbaum discussed some of the continuing challenges faced by NIEHS, including the global impact of environmental health issues, the complexity of disease, the mandate to translate effectively research findings into treatment and prevention, and the need to increase efforts to cross disciplines and look for opportunities for synergy in research.



People in the audience, such as Toxicologist Helen Cunny, Ph.D., center, gave speakers with questions for the new director their undivided attention. (Photo courtesy of Steve McCaw)



Along with the serious and at times moving moments, the talk also featured several humorous moments. Associate Director Chris Portier, Ph.D., center, enjoyed a comment from an audience member. He is shown with Associate Director Marc Hollander, left, and Principal Investigator Karen Adelman, Ph.D. (Photo courtesy of Steve McCaw)

NIEHS Director Honored for Research

The week before she assumed her duties as NIEHS director, Linda Birnbaum, Ph.D., was honored for her research with a 2008 Level III Scientific and Technological Achievement Award (STAA) from the U. S. Environmental Protection Agency (EPA) for a paper published last year. Her study, “[Elevated PBDE Levels in Pet Cats: Sentinels for Humans](#),” appeared in the September 15, 2007 issue of the journal *Environmental Science & Technology (ES&T)*.

As the EPA [website](#) explains, Level III STAA winners are researchers “who have accomplished an unusually notable research or technological effort.” Their research must meet the high standard of making “substantial revision or modification of a scientific/ technological principle or procedure or an important improvement to the value of a device, activity, program or service to the public.”

Birnbaum’s study explored the association between levels of PBDEs (polybrominated diphenyl ethers) in household cats and the incidence of feline hyperthyroidism, which has risen dramatically since the fire-retardant compounds were introduced 30 years ago. Based on their analysis of PBDE concentrations in the serum of household cats, the investigators determined that exposure patterns in cats parallel those of humans, especially children, and that further investigation using cats as a “sentinel species” for humans may help scientists better understand the health effects of chronic exposure to the endocrine-disrupting polybrominated flame retardants.

Receiving the award along with Birnbaum was lead author and EPA Research Biologist Janice A. Dye, Ph.D. The award also acknowledged the contributions of co-authors from Indiana University and the University of Georgia.

During the question-and-answer section, she responded to several pointed questions with a candor that left speakers expressing their encouragement and faith in her willingness to push for greater transparency. In closing, she promised to promote “[effective] leadership, not dictatorship” and thanked the employees for helping her feel at home during her first weeks at NIEHS. “You guys have been so welcoming,” she told the audience.

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Leaders Discuss University of New Mexico Research

By Eddy Ball

A visit last month to Albuquerque, NM, by NIEHS leaders Sam Wilson, M.D., and Allen Dearry, Ph.D., brought together then U.S. Representative and Senator-elect Tom Udall and members of his staff with NIH/NIEHS grantees at the University of New Mexico (UNM). The December 17 meeting featured an information session highlighting NIEHS-funded research and collaborative public health efforts involving the university.

The event was an opportunity to showcase a program that, Wilson explained, “exemplifies the ways cross-disciplinary efforts involving basic, community-based participatory and clinical research can be translated effectively through education and community outreach to impact directly the lives of citizens at their homes and workplaces.”

Representing UNM at the information session were six individuals from across the spectrum of the university’s health sciences leadership:

- Paul Roth, M.D., UNM executive vice president for Health Sciences and dean of the UNM School of Medicine
- John Pieper, Pharm.D., dean of the UNM College of Pharmacy and UNM Health Sciences Center (HSC) vice president for research
- Pope Moseley, M.D., chair of the Department of Internal Medicine at the UNM School of Medicine and deputy director of the [New Mexico Center for Environmental Health Sciences](#)
- Scott Burchiel, Ph.D., associate dean for research and professor in the UNM College of Pharmacy, director of the New Mexico Center for Environmental Health Sciences and [NIEHS center grant](#) principal investigator (PI)
- Stephani Hines, assistant dean for assessment in the UNM College of Pharmacy, environmental health specialist and member of the NIEHS National Advisory Environmental Health Sciences Council
- Johnnye Lewis, Ph.D., director of the UNM NIEHS Center Community Outreach and Education Program and UNM-HSC Community Environmental Health Program and its Diné Network for Environmental Health and PI on NIEHS [risk assessment](#) and [environmental justice](#) grants



The attendees gathered for a photo with the then senator-elect. Shown, left to right, are Lewis, Burchiel, Dearry, Pieper, Udall, Wilson and Hines. (Photo courtesy of Stephani Hines and the UNM College of Pharmacy)

Following remarks by Udall and an NIH/NIEHS overview by Wilson, Pieper underscored UNM institutional commitments to environmental health science. He also talked about collaborative efforts with the Department of Energy, Environmental Protection Agency and other government partners in the state — such as Sandia National Laboratory, Los Alamos National Laboratory, the Lovelace Respiratory Research Institute and the Eastern Navajo Health Board. To give Udall and his staff a better sense of research and translation at UNM, presenters also went into greater detail about a few representative programs.

Burchiel outlined initiatives in exposure biology and border health/asthma research. Hines reported on successful education outreach programs using the student edition of the NIEHS journal *Environmental Health Perspectives (EHP)* to compliment high school and college science curricula. In her talk, Lewis reviewed community-based measures to protect people living on Navajo tribal lands from widespread pollution of water supplies by uranium tailings left over from mining operations — a suspected cause of elevated kidney and related disease among residents of the area.

The final presentation by Moseley underscored UNM successes in integrating environmental health and clinical outcomes. He pointed with pride to nearly two-fold increase in NIH funding for internal medicine research at UNM since 2001 and the rapid expansion of translation of research into the community.

The visit was part of an ongoing effort by the NIEHS senior leadership team to support grantees in the field. The series of site visits and meetings throughout the country initiated by Wilson following his appointment in August 2007 has also helped foster inter-program and interagency partnerships to leverage funding and other resources, as well as raise the profile of NIEHS nationally as the premier environmental public health component of NIH.



Then U. S. Representative Hilda Solis attended a briefing at the University of Southern California in May. (Photo courtesy of Jon Nalick and the USC News)

Impacting Decision Making at the Cabinet Level

Outreach efforts by the NIHS leadership team may well have unforeseen benefits when the new administration's cabinet formally begins work on January 20. During the spring of 2008, President Obama's Secretary of Labor Hilda Solis was one of two U.S. representatives who attended a similar information session on May 27 with Wilson, Dearth, and NIEHS grantees John Peters, M.D., Sc.D., Frank Gilliland, M.D., Ph.D., James Gauderman, Ph.D., Andrea Hricko and Dean Carmen Puliafito, M.D., of the University of Southern California (USC) Keck School of Medicine in Los Angeles.

The [session](#) was a briefing for the representatives about current NIEHS-funded research and new initiatives in the areas of air pollution and children's health. Solis and U. S. Congresswoman Lucille Roybal-Allard both represented areas of Los Angeles, where vulnerable populations, such as children, are exposed to high levels of airborne particulate matter and gases from exhaust.

One outcome of Solis' meeting with Wilson and Peters could well be that the new secretary will be more likely than before to think of NIEHS and the environmental health sciences community as she pursues her advocacy of fair employment practices, environmental justice and health equity in the months and years to come. Like other government representatives who have participated in NIEHS information sessions, Solis may also have a keener sense of the economic development impact of environmental health sciences funding.

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National Children's Study Starts in North Carolina and New York

By Eddy Ball

Following eight years of intensive research and planning on what was described as “a landmark day for a landmark study,” on January 13 NIH launched the National Children's Study at sites in North Carolina and New York. The study will be the largest long-term investigation of children's health and development and their links to the environment ever to be conducted in the United States. The [Eunice Kennedy Shriver National Institute of Child Health and Human Development \(NICHD\)](#) is the lead NIH institute for the study in partnership with NIEHS.

Authorized by Congress in the Children's Health Act of 2000, the National Children's Study will eventually involve 100,000 families over a 21-year period in 105 counties served by an estimated 40 centers nationwide. Biomedical and environmental samples will be stored at a central repository and, along with clinical and lifestyle questionnaire data, will be analyzed to provide insights into the environmental causes of such conditions as birth defects, premature birth, asthma, diabetes, childhood cancers and autism.

In addition to NICHD and NIEHS, other members of the consortium carrying out the study include the Centers for Disease Control and Prevention (CDC) and the U.S. Environmental Protection Agency (EPA).

Speaking for NICHD during the webcast announcement were NICHD Director [Duane Alexander, M.D.](#), and National Children's Study Director [Peter Scheidt, M.D.](#) Describing the initial two of seven projected Vanguard Centers were Principal Investigators [Barbara Entwisle, Ph.D.](#), of the University of North Carolina who will be overseeing recruitment in rural, sparsely populated Duplin County, N.C., and NIEHS grantee [Phil Landrigan, M.D.](#), of the Mount Sinai School of Medicine, who will be in charge of activities in the Borough of Queens, N.Y., where residents speak some 105 languages and about half of the 2.2 million person population were born outside the United States.

“Initially, [the study] will provide major insights into disorders of birth and infancy, such as preterm birth and its health consequences,” Alexander said in his introduction. “Ultimately it will lead to a greater understanding of adult disorders, many of which are thought to be heavily influenced by early life exposures and events.”

During the next 18 months, each of the initial Vanguard Centers will begin recruiting and enrolling approximately 375 women who are pregnant or planning a pregnancy to participate in the study. The study sites and volunteers are being selected as part of a plan to make the study participants representative of the diverse population of the country as a whole. Researchers will collect blood, urine, hair and vaginal swab samples from volunteers, as well as dust, water and air samples from their environments.

During the first two years, contact with participants and their children will include home visits, a visit to the delivery and follow-up telephone interviews. After the third year, participants will receive follow-up visits every three years until the child reaches age 21. There are no current plans to extend the study into adulthood, although webcast participants did not rule out the prospect.



Landrigan, above, described himself as “delighted, almost overwhelmed,” to be a part of the groundbreaking National Children's Study. (Photo courtesy of Phil Landrigan and the Mount Sinai School of Medicine)

Neurobiology Postdoc Awarded Communication Fellowship

By Eddy Ball

This year, Negin Martin, Ph.D., a research fellow in the NIEHS Membrane Signaling Group, is taking a big step forward toward her career goals by participating in an advanced training opportunity in science communication. On January 5, Environmental Health Sciences (EHS) CEO and Chief Scientist John Myers, Ph.D., notified Martin of her selection as one of the organization's 2009 Science Communication Fellows. The award carries with it a stipend and 12 months of experience in a structured internship in science writing for a variety of audiences.

"I love to write," Martin said of the news, "and this is a wonderful opportunity to actually try to do something as a professional. I'll be working closely with a science editor who can help me improve my writing." A native of Iran, Martin said she will also appreciate the additional opportunities to develop her facility in her second language.

By the end of her [fellowship](#), Martin will have a portfolio showcasing examples of her accomplishments communicating environmental health research to the media, policy makers and the public. She plans to build on her fellowship experience as part of her career development at NIEHS to move ultimately into a research post that combines time at the bench with science writing and editing.

Each month, the EHS fellows will identify two important new scientific findings within their areas of expertise, submit for critique and post summaries of those findings, and report on those findings during monthly conference calls. Martin and her colleagues will also write brief commentaries for the Media Reviews section of the EHS publication [Environmental Health News](#).

As part of her fellowship experience, Martin will also enjoy several additional networking opportunities, including a two-day training meeting, which will likely be held in Washington. Following the year-long active training, she will continue to be an EHS Science Communication Fellow in the growing network of trained science communicators and serve as a mentor for succeeding fellows.

Martin is currently a research fellow in the NIEHS Laboratory of Neurobiology working with Principal Investigator David Armstrong, Ph.D., who was honored in 2007 as NIEHS Mentor of the Year. She recently completed five years as an Intramural Research Training Award (IRTA) fellow and accepted an appointment as a research fellow.

Her research focuses on the molecular mechanism and effects of environmental toxins on the thyroid hormone system. She is particularly interested in outlining the molecular components of rapid thyroid hormone signaling in the brain.

Martin earned her Ph.D. in Biochemistry from the School of Medicine and Dentistry at the University of Rochester and joined NIEHS after training for two years as a postdoctoral fellow in the Department of Medicine at Duke University.



Martin has also been honored with NIH Fellows Award for Research Excellence (FARE) awards in 2004 and 2007, the Elon-Huntington Hooker Graduate Fellowship award in 1999 and the Walter S. Bloor Award for outstanding Ph.D. candidate in Biochemistry in 2001. (Photo courtesy of Steve McCaw)

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Robertson Chairs SLA Centennial Commission

By Eddy Ball

NIEHS Library Director Dav Robertson is excited about the 100th anniversary of the Special Libraries Association (SLA) and his appointment as chair of the 2009 Centennial Commission. This winter he is involved in SLA events that will culminate June 14 – 17 when the group holds its Annual Conference in Washington. The conference will feature a keynote address by former Secretary of State Colin Powell and an Annual Awards Reception at the Great Hall of the Library of Congress.

Robertson kicked off the centennial locally on December 4, 2008 with his keynote address on “InfoPrognostications, 1909 – 2109” to members of the North Carolina chapter gathered in Chapel Hill. He also attended the SLA Leadership Summit 2009 on January 14 – 17 in Savannah, Ga., where representatives of state chapters, division chairs and members of the Centennial Commission met to prepare for the Annual Conference.

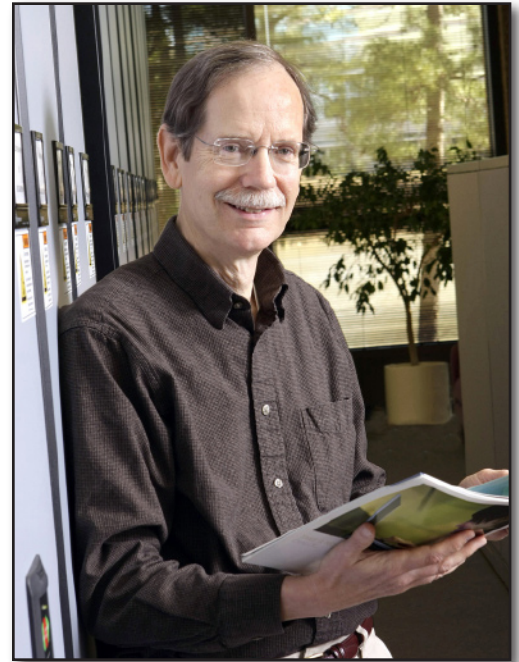
According to Robertson, the [SLA Centennial](#) celebrates the distinctive character of the organization’s mission. Unlike most academic or public archival libraries, the role of special — or “specialized” — libraries like the one at NIEHS, Robertson explained, “is not education per se but the delivery of practical, focused and timely information to the executives and other clients within their organizations.”

Over the past 100 years, SLA membership has grown to include 11,000 librarians, or what Robertson prefers to call “information professionals,” in 75 countries. The organization strives to provide cutting-edge continuing education and networking opportunities for members and serves as an advocate for specialized libraries.

As their organizations and operating environments change over time, specialized libraries must be proactive as they evolve to meet new needs and take advantage of new resources — forcing them to adopt what Robertson described as an “entrepreneurial” orientation toward collaboration with their users. “We embrace change,” Robertson maintained, “and use our knowledge and vision to further the goals of our organizations.”

“The more we’re involved in SLA and other associations,” Robertson concluded, “the more we find out about other resources, new products and services, and other collections that we can then use to answer questions from our scientists.”

SLA was founded in 1909 by librarians who thought that libraries serving business, government, social agencies and parts of the academic community were different from other libraries. Because of their specialized interests, the librarians felt a need to establish a unique kind of professional development organization. According to Robertson, the kind of proactive, user-involvement orientation fostered by SLA has been instrumental in helping the NIEHS Library improve information services for the Institute’s researchers in several important ways ([see text box](#)).



Robertson, above, stands beside one of the many indications of the evolution of the specialized NIEHS Library to an electronically based information provider — the compact shelving that holds its down-sized print holdings. (Photo courtesy of Steve McCaw)

Keeping Abreast Benefits Scientists at NIEHS

Networking with their colleagues at SLA and other organizations has helped NIEHS information professionals better serve their users.

- Initiating cooperative purchasing agreements with other members of the NIH Consortium of Libraries (NIHCOL), giving NIEHS scientists online access to such resources as all of the Nature journals, the Web of Science, QUOSA and UptoDate at a fraction of the cost of individual subscriptions
- Keeping users up to date on changes to PubMed and other National Library of Medicine resources, as well as science databases being updated or developed, such as the Elsevier BrainNavigator
- Enhancing the subject matter knowledge of “embedded” librarians through such activities as attendance at neuroscience conferences and training in epidemiology to better understand scientists’ information needs
- Developing with colleagues in the Medical Library Association (MLA) more video-based training for individual needs
- Enhancing the profile of NIEHS through involvement in SLA subject divisions devoted to environment and the biomedical and life sciences
- Exploring with the Renaissance Computing Institute the possible future acquisition of a touch-sensitive “vis-wall” display for distance conferencing and collaborations
- Establishing relationships with sister agencies within the Department of Health and Human Services
- Taking the lead in mentoring and career development for information professional interns and junior scientists, which led to the creation of the SLA’s Rose L. Vormelker Award for mentoring. NIEHS Biomedical Librarian Larry Wright, Ph.D., was the first member honored with the award in 1998.

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Distinguished Guest Gives Disability Presentation

By Eddy Ball

On January 13, the NIEHS Diversity Council Disability Advocacy Committee (DAC) welcomed as its keynote speaker one of the highest ranking officials with a disability in the federal government today, Special Assistant to the Assistant Attorney General for Civil Rights in the Department of Justice (DOJ) Ollie Cantos, J.D. Cantos, who is blind because of medical complications at birth, addressed NIEHS employees with a presentation titled “Employment of People with Disabilities: A Practical Approach.”

DAC members were joined at the event by NIEHS Associate Director for Management Marc Hollander, who introduced the speaker, and Acting Director Sam Wilson, M.D., who presented closing remarks. DAC Co-chair J. J. Bell-Nichols welcomed the audience, DAC member Jennie Foushee provided piano accompaniment, and DAC Chair Alicia Moore presented Cantos with tokens of appreciation following the talk.



“When we look at disability, we look at the reality that it is simply a characteristic,” Cantos contended, “one of thousands of characteristics that we each happen to possess.” (Photo courtesy of Steve McCaw)

Cantos, who would spend the final part of his talk discussing ways to build good will and networks, opened his engaging presentation by complimenting his audience on the “incredible work that NIEHS continues to do” — both in terms of its scientific excellence and its commendable track record in hiring and accommodating qualified workers who have disabilities.

During his presentation, Cantos carefully built up support for his closing challenge to NIEHS to “become a beacon for other agencies” to follow as they reach out to the community of people with disabilities. He asked everyone in the audience to “think about how you can be an instrument of change for the better.”

“Each of us,” Cantos argued, “must look at the way people with disabilities can contribute meaningfully to the workplace just like anyone else.” Dismissing the notion that people with disabilities are limited to performing what he called “disability work,” Cantos asserted, “People with disabilities can do everything from cleaning the office to running it.”

Integrating the talents of people with disabilities into NIEHS and other agencies, he said, makes “good business sense” and can help impact the alarming 38 percent unemployment rate of people with disabilities. Cantos was prepared with the web addresses of a number of organizations capable of helping employers learn how to recruit, employ and accommodate individuals with disabilities.

Cantos made a point of addressing issues related to “those with disabilities that are not readily apparent.” Some of these disabilities, such as autism, he said, can actually help a worker perform critical, detail-oriented tasks much more accurately. Cantos also dismissed concerns about the potential of violent behavior by workers with psychiatric disabilities, observing that “99.99 percent” of persons with psychiatric disabilities are not a danger to others in the workplace.

Cantos' theme throughout his talk centered on “the things we have in common with one another, regardless of whether we have a disability — namely [that] there are challenges in our lives, we work on conquering those challenges accordingly, [and] then we learn from past mistakes and tackle new challenges.” People with disabilities often face an added challenge, however, because of the “myths that surround” various disabilities.

Several in the audience soon discovered firsthand how baseless some of the myths that Cantos described can be as he turned confidently with marker in hand to a flip chart beside him. During the rest of his talk, Cantos underscored his message with words and diagrams that he entered almost flawlessly on a surface he could not even see.



In his introduction, Hollander, center, shown with Bell-Nichols to his right, described Cantos as “an incredible and accomplished man” who “achieved an important milestone by becoming a presidential appointee at the age of 37.” (Photo courtesy of Steve McCaw)



Several people in the audience were surprised by the quality of Cantos' penmanship, which was more legible than the writing of some sighted graduates of the world's leading medical schools. (Photo courtesy of Steve McCaw)



Wilson emphasized that “it's critically important that we have events like this to allow us to think about fresh approaches for tapping into the unique potential of every member of our [NIEHS] family.” (Photo courtesy of Steve McCaw)



Moore, center, thanked Cantos for his visit to NIEHS and inspiring message. Foushee, background left, was ready to play the piano as the audience left the auditorium. (Photo courtesy of Steve McCaw)

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Superfund Grantees Begin Work on Documentary Series

By Melissa Fabiano-Scheuer

With support from the NIEHS Superfund Basic Research Program (SBRP), researchers at the University of California, San Diego (UCSD) are following a road less traveled in order to translate their scientific research into policy and public health information. Working with the UCSD-TV Public Affairs Office, researchers Keith Pezzoli, Ph.D., and Hiram Sarabia are now at work on a television documentary inspired by a special tour they conducted for attendees at the 2008 American Public Health Association annual conference, “Public Health without Borders,” held in San Diego October 25-29, 2008.

Pezzoli and Sarabia’s research stresses the importance of furthering global environmental health partnerships related to vulnerable tribal communities and the sustainable development of low-income settlements on the U.S.-Mexico border.

The documentary, focusing on global environmental health (GEH) issues, will incorporate the tour of the San Diego-Tijuana U.S.-Mexico border and is projected to air during the fall of 2009. The APHA tour was led by UCSD’s Urban Studies and Planning Program and the Center for Iberian and Latin American Studies (CILAS) in partnership with Peter Ashley, Dr.PH., of the U.S. Department of Housing and Urban Development, Jenny Quintana, Ph.D., of San Diego State University’s Graduate School of Public Health, and Oscar Romo of the National Oceanic and Atmospheric Administration (NOAA).

The tour highlighted the impacts of rising irregular settlements and rapid population growth in the city of Tijuana, with particular emphasis on the public health and ecological impacts of environmental toxicants and cross-border flows in the border region.

The documentary’s ultimate goal is to increase public awareness of these important issues and highlight international collaboration and local efforts to protect the regions’ public health and coastal ecosystems from environmental toxicants.

As their studies continue, Pezzoli and Sarabia maintain efforts to work in conjunction with tribes, government agencies, researchers and community organizations on both sides of the U.S.-Mexico border. This collaborative network builds on the groundbreaking work of the University of Arizona’s SBRP and U.S.-Mexico Binational Center for Environmental Studies and Toxicology. Pezzoli and Sarabia’s current research highlights GEH



The tour organizers, foreground, are shown with the APHA tour group at the U.S.-Mexico border. (Photo courtesy of Hiram Sarabia and UCSD)



The new fence snakes along the border separating California and Mexico. (Photo courtesy Hiram Sarabia and UCSD)

challenges, emphasizing environmental exposure to pathogens and toxicants, sustainable communities, and ecosystems. The U.S.-Mexico border poses unique challenges, in part, because its watersheds are bisected by international boundaries. This makes it difficult to manage waste flows, ecosystems, and scarce natural resources like water.

In addition to Pezzoli and Sarabia's research on the U.S.-Mexico border region, they and their colleagues at UCSD will work along with the Global Planning Educators Interest Group, Worldwide Universities Network and Scripps Institution of Oceanography to promote sustainable city-region development in other parts of Latin America and beyond. The documentary they are working on, the first in a series, will focus on integrated research and action to address issues at the water/climate/poverty nexus in vulnerable human settlements along the U.S.-Mexico Border.

(Melissa Fabiano-Scheurer is a communications specialist for MDB, Inc., a contractor for the NIEHS SBRP and the Worker Education and Training Program. She is a regular contributor to the *Environmental Factor*.)

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UC Davis Study Examines Rise in Autism Rates

By Eddy Ball

A new analysis of data on autism performed by NIEHS grantees at the University of California Davis (UCD) undermines arguments that California's dramatic 7- to 8-fold increase in autism cases may be largely due to changing diagnostic practices of physicians. The researchers, who are affiliated with the UCD Department of Public Health Sciences and the UCD Medical Investigation of Neurodevelopmental Disorders (M.I.N.D.) Institute, found that including milder cases, performing earlier diagnosis and demographic factors can explain only a small part of the rise in the number of children with the disorder.

In their [study](#), which was published in the January issue of *Epidemiology*, epidemiologist [Irva Hertz-Picciotto, Ph.D.](#), and programmer analyst Lora Delwiche examined data on autism cases from 1990 through 2006 gathered by the California Department of Developmental Services, along with data from the United States Census Bureau and the California Department of Public Health's Office of Vital Statistics. Their findings offer new insight into the alarming increase in prevalence and point to environmental causes as the most productive direction for future research.

According to the researchers, the increase was not simply a result of California's continuing influx of new residents from elsewhere, earlier detection or the inclusion of milder cases. Taken together, these factors accounted for less than one-seventh of the increase, which the authors described as "a major public health and educational concern" that shows no sign of abating.

An increasingly diverse population was also not to blame, observed lead author Hertz-Picciotto in interviews following release of the study, since the disorder occurs among different ethnic groups at similar rates. It is also unlikely that families with autistic children moving to California had a significant impact on the rise.

For Hertz-Picciotto, the increase underscores the need for greater emphasis on investigating further the role of environmental causes of the disorder. "Right now, about 10 to 20 times more research dollars are spent on studies of the genetic causes of autism than environmental ones," she said. "We need to even out the funding."

Hertz-Picciotto is involved in two large NIEHS-funded epidemiology studies currently underway at the [M.I.N.D. Institute](#) aimed at discovering the causes of autism. The [Childhood Autism Risk from Genetics and the Environment \(CHARGE\)](#) study is a major investigation of environmental factors and gene-environment interactions in the disorder involving 2,000 children, including 700 children with autism. The [Markers of Autism Risk in Babies-Learning Early Signs \(MARBLES\)](#) will follow mothers of a child with autism through a subsequent pregnancy to uncover early markers that may predict outcome of the pregnancy.

Citation: Hertz-Picciotto I, Delwiche L. 2009. The Rise in Autism and the Role of Age at Diagnosis. *Epidemiology* 20(1): 84-90.

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Former Postdoc Joins Biotech Management Team

By Eddy Ball

In December 2008, Cellular Dynamics International (CDI) of Madison, Wis. announced the appointment of three new executives, including former NIEHS Postdoctoral Fellow Emile Nuwaysir, Ph.D., to lead the company as it attempts to industrialize stem cell technologies after raising \$18 million in venture capital. Nuwaysir, who is the company's chief operating officer and one of its vice presidents, will be responsible for product development, manufacturing and quality systems.

Founded in 2004, [CDI](#) describes itself as a leading developer of next-generation stem cell technologies for drug development and personalized medicine applications. CDI harnesses the power of pluripotent stem cells and their ability to differentiate into any cell type for world-class drug development tools.

Nuwaysir was a postdoctoral researcher at the National Human Genome Research Institute and the NIEHS, where he helped establish the laboratory that became the [National Center for Toxicogenomics](#). Before leaving NIEHS in 2000, Nuwaysir worked with then Scientific Director Carl Barrett, Ph.D., and Cynthia Afshari, Ph.D., to develop the [ToxChip](#) in the NIEHS Microarray Center, now directed by Rick Paules, Ph.D., who was co-director during Nuwaysir's tenure at the Institute.

Prior to joining CDI, Nuwaysir served as senior vice president of Program Management and Business Development and chief technology officer within Roche Diagnostics at the Roche NimbleGen business unit. He was responsible for overall management of the R&D portfolio and product life cycle, as well as outward-facing licensing and business development activities.

While at NimbleGen, Nuwaysir served in various scientific and managerial roles at the biotech startup, including Vice President of Business Development, Marketing, and Product Development, and R&D Group Leader. He was the first employee hired at NimbleGen and a key member of the management team that built the company and eventually sold it to Roche Diagnostics.

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*Nuwaysir in his office at NIEHS
(Photo courtesy of Steve McCaw)*

The Role of MAPK Pathways in Metastasis

By Robin Arnette

The mitogen-activated protein kinase (MAPK) pathways are signal transduction cascades that regulate gene expression, cell growth and development, and apoptosis or cell death. The NIEHS Distinguished Lecture Series on December 9, 2008 brought to NIEHS one of the nation's leading experts on the enzymes that make up the MAPK pathways in mammalian cells, Gary L. Johnson, Ph.D., professor and chair of the Department of Pharmacology at the University of North Carolina School of Medicine.

In his talk, Johnson explored the “Function of MAPK Signaling Networks: From Metastasis to Tissue Stem Cells.” A group of principal investigators from the Laboratory of Signal Transduction — John Cidlowski, Ph.D., James Putney Jr., Ph.D., and Perry Blackshear, M.D., D.Phil. — hosted the event.

MAPK pathways are vitally important to living organisms, and [Johnson](#) pointed out that mutations in any of the proteins that comprise these pathways in humans may lead to illnesses such as cancer, cardiovascular disease and autoimmunity. He also explained that in humans there are 11 MAPKs, seven MAPK kinases (MKKs) and 21 MAPK kinase kinases (MKKKs). “One of the main questions I wanted to answer early in my research career was why there were so many MKKKs and fewer MKKs and MAPKs,” Johnson said. “The reason is they have different functional protein interaction domains and different motifs, which means these enzymes have different functions depending on the cell type in which they are expressed.”

The type of cellular stress also determines which enzymes are expressed. Johnson said that oxidative stress, DNA damage via radiation, or a pharmaceutical compound, for example, activates different kinase pathways. Research using UV radiation or osmotic stress on cells determined that six different MKKKs regulate other kinases within the signaling network.



Cidlowski introduced Johnson and monitored questions from the audience after the talk. (Photo courtesy of Steve McCaw)



Johnson said, “My lab’s future work will involve targeting specific MKKKs or families of MKKKs with small molecules to selectively inhibit stimulus-specific activation of networks in gene expression.” (Photo courtesy of Steve McCaw)

Johnson's lab used gene targeting to characterize 13 of the 21 MKKKs, and he discussed one of these proteins, MEKK1, in detail. His team made MEKK1 knockouts and discovered that it was the only characterized kinase to date that had E3-ligase activity and was adjacent to a modified cysteine-rich region known as a SWIM domain. Johnson added MEKK1 back into the knockouts, and confocal imaging determined that MEKK1 was most abundant on actin fibers.

Since metastasis requires several steps such as vascularization, growth and proliferation of a primary tumor, MEKK1's localization to actin fibers seemed to corroborate other experimental findings. For instance, the team used a polyoma middle-T mouse model and found that MEKK1 regulated tumor cell invasiveness. Other studies demonstrated that MEKK1 regulated calpain, a caspase-like protease, which regulated two other proteins that are involved in focal adhesion and the association of the cytoskeleton with focal adhesion complexes. "MEKK1 is regulating through Jun kinase and externally regulated kinase (ERK)/calpain activity, and that's regulating the turnover of these focal adhesion complexes," Johnson explained.

Johnson also talked about another MKKK his lab characterized, MEKK4. It was highly expressed in the embryo and the trophoectoderm, the first differentiated tissue from the embryo and trophoblast stem cells. The MEKK4 stem cell knockout phenotypes were similar to those of MEKK1, but when Johnson's team mutated one amino acid in the active site, the new MEKK4 knock-in lacked kinase activity. Further studies indicated that Jun kinase or p38 inhibitors could mimic the up-regulation of a number of the genes that were altered in MEKK4 kinase-inactive trophoblast stem cells. "There are epigenetic changes in the MEKK4 knock-in trophoblast stem cells such as a loss of acetylation of lysine 5 at histone 2A and loss of acetylation of lysine 5 at histone 2B."

Johnson ended his talk by listing four major conclusions from his work with MKKKs:

- They function as signaling hubs for the selective control of the MAP kinase network
- They regulate gene expression much differently than just by the activation of a MAPK and phosphorylation of a substrate
- They regulate the repertoire of required transcription machinery
- They control epigenetic modification of chromatin

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Columbia University Researcher Discusses Mitochondrial Disorders

By Robin Arnette

On January 13, Salvatore DiMauro, M.D., a leading researcher in the study of mitochondrial disorders, gave a distinguished lecture at NIEHS titled “Mitochondrial Medicine.” The talk provided an overview of the progress that has been made in the study of defects in mitochondria, tiny organelles found in every cell of the body. Commonly known as “powerhouses of the cell,” mitochondria generate the energy that sustains life and supports growth and defects in these important organelles cause a variety of physiological problems.

Symptoms include neurological problems, developmental delays and learning disabilities. The [Mitochondrial Disease Action Committee](#) reports that many diseases of aging may be attributed to defects in mitochondrial function, such as type 2 diabetes, Parkinson’s disease, stroke and Alzheimer’s disease. [DiMauro](#), the Lucy G. Moses Professor of Neurology at Columbia University Medical Center, reiterated the importance of mitochondria in eukaryotic organisms and also traced their curious beginnings.

“One-and-a-half billion years ago, free-living bacteria took up residence in primordial eukaryotic cells, and this arrangement became permanent,” DiMauro said. “Mitochondria are the only organelles that don’t come from us and as a result have their own DNA.”

Although mitochondrial DNA (mtDNA) is a small, double-stranded, circular piece of DNA, the number of bases it contains is similar to that found in eukaryotic nuclear DNA. mtDNA encodes 13 subunits of the electron transport chain, which is responsible for generating energy for the cell in the form of adenosine triphosphate (ATP). Mitochondrial genetics differs from Mendelian genetics in three ways:

- inheritance — exclusively from the mother
- heteroplasmy — a single cell containing both mutant and normal mtDNA
- mitotic segregation — random change in the degree of heteroplasmy, possibly accompanied by a change in clinical phenotype, in subsequent generations of cells



According to the [United Mitochondrial Disease Foundation](#), where DiMauro is a trustee, every 30 minutes a child is born who will develop a mitochondrial disease by the age of 10. (Photo courtesy of Steve McCaw)



NIEHS Laboratory of Molecular Genetics (LMG) Principal Investigator Bill Copeland, Ph.D., fielded questions from the audience. He and Kristine Witt, M.Sc., a toxicologist in the NTP Toxicology Branch, co-hosted the seminar. (Photo courtesy of Steve McCaw)

DiMauro explained that mtDNA mutations fit into two categories: single deletions in mtDNA or point mutations in tRNA genes that impair overall mitochondrial protein synthesis. Single deletions of mtDNA can cause Kearns-Sayre Syndrome (KSS), Chronic Progressive External Ophthalmoplegia (CPEO) or Pearson syndrome, while two of the most common point mutations in tRNA genes cause MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke) and MERRF (myoclonic epilepsy associated with ragged red fibers). Point mutations in protein-coding genes cause specific enzyme defects.

A muscle biopsy from patients with either MELAS or MERRF shows fibers with purple patches, which denote proliferation and accumulation of mitochondria. DiMauro said that mitochondrial proliferation was probably a futile attempt to compensate for the mitochondrial respiratory chain defect. Even though the two disorders overlap, they are different syndromes and clinicians have no difficulty distinguishing between them, but DiMauro and his colleagues are still trying to understand their pathogenesis.

“In MELAS there is a mutation in the tRNA leucine and in MERRF the mutation is in the tRNA lysine,” DiMauro said, “so the consequence should be the same — a decrease in ATP production. The fact that they are different syndromes is still unexplainable.”

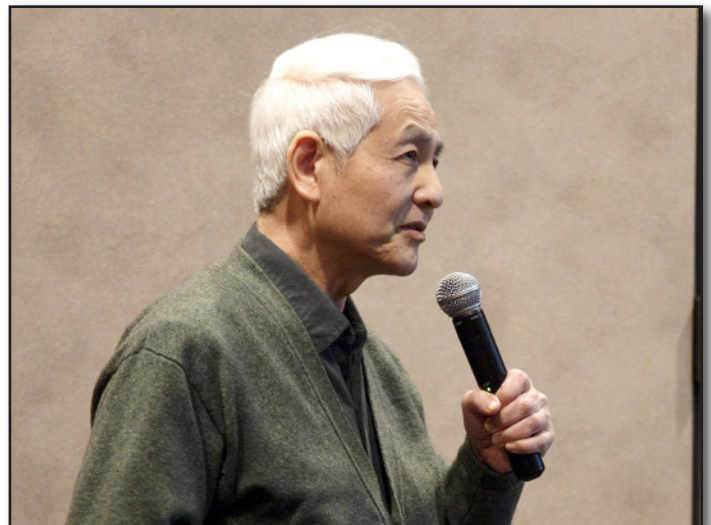
There are several areas, however, in which mitochondrial research has been quite successful. DiMauro’s group described the mutations in two genes involved in the biosynthesis of coenzyme Q10 (CoQ10, ubiquinone) that lead to CoQ10 deficiency. As a result, DiMauro and colleagues can treat these diseases, which usually cause encephalomyopathy. “High doses of CoQ10, taken orally, make these patients better or in some cases cures them,” he said.

DiMauro ended his talk with work that may be of great importance to medicine. Recent research suggests that mitochondria actually move around in all cellular tissues. This movement is essential for the balance of energy distribution within the cell. He said, “If you restore mitochondrial motility, you may be able to successfully treat a lot of diseases.”

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Chief of the NIEHS DNA Repair & Nucleic Acid Enzymology Group and former Deputy Director/Acting Director Sam Wilson, M.D., had questions for the speaker. Seated behind Wilson was LMG Chief Jan Drake, Ph.D. (Photo courtesy of Steve McCaw)



NIEHS Neuropharmacology Group Chief Jau-Shyong (John) Hong, Ph.D., also had a question. Hong was interested in DiMauro’s perspective on the causes of Parkinson’s disease. (Photo courtesy of Steve McCaw)

Study Offers Insight into Endocrine Disruption by Soy

By Eddy Ball

NIEHS-supported researchers report compelling new evidence about the mechanisms linking genistein supplementation during development of mice to altered DNA methylation patterns that can lead to serious health complications later in life, according to a study published in the journal *Endocrinology*. The researchers identified novel uterine genes whose expression was altered by neonatal exposure to genistein (GEN) and diethylstilbestrol (DES) – an estrogenic chemical with well documented adverse transgenerational carcinogenic and reproductive effects.

Led by NIEHS grantee and Chair of the Department of Environmental Health at the University of Cincinnati (UC) [Shuk-mei Ho, Ph.D.](#), and NIEHS Reproductive and Developmental Toxicologist Retha Newbold, the team also included UC Research Associate and NIEHS grantee [Wan-Yee Tang, Ph.D.](#), who was first author on the study, and NIEHS Reproduction Group Biologist Wendy Jefferson, Ph.D.

According to an editorial published in the same issue of *Endocrinology*, the [study](#) marks the first time specific molecular evidence has been identified that supports the theory of a two-step process for epigenetic alterations triggered by endocrine disruption. Only one of the 14 uterine genes identified in the study had been previously characterized in the rodent uterus.

Animals in the study were housed according to NIEHS/NIH guidelines and fed NIH-31 laboratory mouse chow that tested negatively for estrogenic activity. By including a control group of mice that underwent ovary removal prior to puberty in their experiments, the investigators demonstrated that the process is dependent upon the presence of postpubertal ovarian steroids.

This finding adds important evidence for the argument that repressed epigenetic memories or “imprinting” of prenatal DES/GEN exposures during neonatal development may be triggered by a “second hit” of estrogen or estrogen-like compounds after puberty or as individuals age — setting up gene expression patterns favorable to tumor development and growth.

The study utilized unbiased methylation-sensitive restriction fingerprinting to determine differentially methylated gene sequences associated with neonatal exposure to DES/GEN. “These genes encode proteins involved in signal transduction, receptor activation, tumor angiogenesis, cell proliferation, apoptosis, intracellular trafficking, DNA repair and chromatin remodeling,” the authors wrote. “A tight association between gene silencing and gene methylation, and the reverse, was observed.”



First author Wan-Yee Tang of the University of Cincinnati (Photo courtesy of Shuk-mei Ho)



Newbold, above, has been a leader in endocrine disruption research at NIEHS. (Photo courtesy of Steve McCaw)

Of the 14 genes influenced by exposure, the team chose one, *nucleosomal binding protein 1 (Nsbp1)* for further analysis because of its central role in chromatin remodeling and transcriptional activation. “The purported functions of *Nsbp1*,” the investigators continued, “together with our current finding that the expression of *Nsbp1* is under estrogen-mediated epigenetic regulation, have led us to speculate that *Nsbp1* may participate in the tumorigenesis of the mouse uterus after neonatal exposure to DES/GEN.”

The [editorial](#) in *Endocrinology* by University of Illinois at Chicago physiologist Gail Prins, Ph.D., noted that the findings could impact current practices regarding soy consumption by mothers and their infants. Depending on the timing of exposures to the phytoestrogen, the epigenetic alterations triggered by DES/GEN exposure during development could potentially offset the widely valorized chemoprotective and beneficial effects of soy consumption.

More completely understanding such timing, Prins concluded, is one of “many things that remain to be done.” The study has set the direction for future studies to identify “secondary triggers for repressed epigenetic memories aside from just hormones,” she continued, and to “formulate an ‘epigenetic fingerprint’ consisting of multiple genes that may be similar or unique for the separate estrogenic compounds, end organs or second hits.” Such information could prove useful in early diagnosis or intervention, she concluded.

Citations: [Prins GS](#). 2008. Estrogen imprinting: when your epigenetic memories come back to haunt you. *Endocrinology* 149(12):5919-5921.

[Tang WY](#), [Newbold R](#), [Mardilovich K](#), [Jefferson W](#), [Cheng RY](#), [Medvedovic M](#), [Ho SM](#). 2008. Persistent hypomethylation in the promoter of nucleosomal binding protein 1 (*Nsbp1*) correlates with overexpression of *Nsbp1* in mouse uteri neonatally exposed to diethylstilbestrol or genistein. *Endocrinology* 149(12):5922-5931.

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Along with her duties as department chair, Ho, above, is director of the Center for Environmental Genetics and co-leader of the Hormonal Malignancies Program in the Joint Cancer Center at the UC College of Medicine. (Photo courtesy of Shuk-mei Ho)



NIEHS Reproduction Group Biologist Wendy Jefferson (Photo courtesy of Steve McCaw)

Trainees Host Stress-Induced Mutagenesis Seminar

By Brian Chorley

On January 5, the NIEHS welcomed Susan Rosenberg, Ph.D., a professor at the Baylor College of Medicine, who conducted a thought-provoking seminar regarding DNA mutation in response to environmental stress. Libertad García Villada, Ph.D., a visiting fellow in the NIEHS Laboratory of Molecular Genetics (LMG) Spontaneous Mutation and DNA Repair Group, coordinated the morning's lecture. The seminar was part of an ongoing series of trainee-hosted speakers organized by members of the LMG Trainee Action Committee (TAC).

[Rosenberg](#), an expert on bacterial models of mutation, has dedicated much of the past decade to understanding mechanisms of strand breakage, recombination and subsequent mutation in response to stress. Rosenberg's talk had an overarching theme of "what's interesting to us is genome instability – how it works and its implications for biology," which, she said, describes her laboratory's core mission.

Genetic variation in a population, Rosenberg explained, gives rise to enhanced adaptation in a changing environment, a concept that is the basis of modern evolutionary theory. She postulated that this variation may arise from two separate sources – pre-existing mutations that may confer adaptation as a stressor is applied or, intriguingly, mutagenesis that confers an adaptive response *after* a stressor is applied.

Rosenberg believes cells run programs that create mutations, some of which ultimately assist in adaptive response to the environment. She explained that when this idea first surfaced, many scientists worried that it supported the arcane notion of Lamarckian evolution – a theory popular in the 19th century that states adaptation is acquired through the concerted efforts of an organism, as in the archetypical scenario of a giraffe's evolving neck length to better reach the leaves of a tree. Although mutation itself is random, with no regard for what adaptation is required, Rosenberg said, "mutagenic *response* is not insensitive to the environment."

During her talk, Rosenberg concentrated on what she described as three core mechanistic principles of stress-induced mutagenesis, all of which may enhance cell or organism "evolvability." The first occurs when an organism senses maladaptation to its environment and switches to a mutagenic state induced by stress response. With the second, mutation is localized to small, presumably random regions of the genome, targeting local gene clusters and avoiding change to the genome



Rosenberg said she was excited to catch up with the people at what she described as "Mutagenesis Central" – certainly a compliment for an institute with so many investigators devoted to mutation research. (Photo courtesy of Steve McCaw)



The LMG was well represented in the audience by scientists with similar research interests, such as Postdoctoral Fellow Stephanie Nick McElhinny, Ph.D. (Photo courtesy of Steve McCaw)

in its entirety. The third involves the differentiation of cellular subpopulations that are transiently hypermutagenic.

Using bacterial models of growth-component deficiency adaptation, Rosenberg's laboratory generated data to support these theories. The investigators found in their models that mutagenesis primarily occurs in regions of double-strand break repair. However, mutation was not constant; rather, it happened only during periods of stress. Rosenberg discovered that the normal high-fidelity, non-mutagenic DNA repair is switched to low-fidelity, error-prone repair governed by the bacterial stress-response factor RpoS and mediation of the translesion synthesis (TLS) DNA polymerase DinB. Because mutation seems to be confined to areas of double-strand break repair, stress-induced mutagenesis is limited to those areas of the genome in which this type of damage has occurred.

According to Rosenberg, two additional signaling mechanisms mediate stress-induced mutagenesis in her models — the SOS and RpoE stress responses. When both are active along with the RpoS pathway, cells transition into a transient hypermutable state. Preliminary evidence generated by her laboratory suggests that these subpopulations are in a ready state and become responsively mutagenic, and therefore most adaptive, when an environmental stressor is applied. Rosenberg explained that little is known about this state and it may well be confined to certain bacteria; however, she said it is tantalizing to speculate about the existence of similar mechanisms in other cell populations.

Rosenberg envisions that her research will have implications beyond the mechanisms of bacterial evolution. An important human corollary is tumor cell responsiveness to chemotherapy. Cancer treatments are primarily anti-proliferative and by design cause cellular stress. As in bacteria, this may activate stress-induced mechanisms in tumor cells that allow for adaptation to these therapies. Application of what Rosenberg coined as “anti-evolution” therapies that suppress these stress-induced mechanisms in tumors may dilute or entirely preempt resistance to chemotherapy.

(Brian Chorley, Ph.D., is a postdoctoral fellow in the NIEHS Laboratory of Molecular Genetics Environmental Genomics Group.)

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Many senior investigators attended the trainee-hosted seminar, including LMG Chief Jan Drake, Ph.D. (Photo courtesy of Steve McCaw)



After the lecture, Rosenberg and host Libertad García Villada (left) fielded questions for nearly 20 minutes from an inquisitive audience. (Photo courtesy of Steve McCaw)

Nano Research Pioneer Speaks at NIEHS

By Eddy Ball

Duke University nanomaterials specialist Mark R. Wiesner, Ph.D., made his first visit to NIEHS on January 9 as a guest lecturer in the Frontiers of Environmental Sciences series. His talk, “Reducing Uncertainty Surrounding Environmental Risks of Nanomaterials: Assessing Transport and Transformation,” kicked off the 2009 series, which was hosted by National Toxicology Program (NTP) Deputy Program Director for Science Nigel Walker, Ph.D.

Wiesner is a professor of Civil and Environmental Engineering in Duke’s Pratt School of Engineering. He also serves as director of the university’s new [Center for the Environmental Implications of NanoTechnology \(CEINT\)](#) — part of a consortium that includes Carnegie Mellon University, Howard University and Virginia Polytechnic Institute and State University and works closely with other domestic collaborators and international partners in Europe, China and South America.

Wiesner devoted the first half of his talk to describing the multi-faceted research planned or already underway at CEINT in its three “theme” and three core areas. These areas range from nanomaterial transport and transformation in laboratory systems to modeling complex and dynamic interactions of nanomaterials with the environment to assess risk.

The center is studying natural, incidental and manufactured nanomaterials and creating mesocosms in Duke Forest to more accurately simulate real-life environments for studying the impact of nanomaterials’ life cycle on ecosystems. The interdisciplinary research teams are also trying to estimate what future production levels may be as a basis for better understanding potential levels of exposure.

“We tend to do what I call ‘bubble-up research,’” Wiesner observed. “We start with very simple systems, and we try to build up to the complex — adding more and more solutes and organics that can interact with the nanomaterials, adding an organism that takes those materials up, then looking at multiple organisms and transfers through trophic levels all the way up to try to build a whole ecosystem, and looking for mechanisms all along the way.”



When Walker introduced the speaker, he noted that the new Center for the Environmental Implications of NanoTechnology headed by Wiesner will “increase the amount of research going on in the area in terms of nanotechnology.” (Photo courtesy of Steve McCaw)



Wiesner introduced the central paradox of his research early in the talk. “Unfortunately, the things that make nanomaterials so interesting to us,” he explained, “are precisely the factors that make them potentially dangerous.” (Photo courtesy of Steve McCaw)

Although the center is funded by the National Science Foundation and U. S. Environmental Protection Agency, researchers there are also collaborating with NIEHS grantees. These include Duke University Superfund Basic Research Center Director [Rich Di Giulio, Ph.D.](#), and [Andre Nel, M.D., Ph.D.](#), chief of the new Division of NanoMedicine at the University of California Los Angeles.

For the second part of his talk, Wiesner turned to work in his own lab on nanomaterial transformations with a focus on the aggregation of nanomaterials and factors that control their mobility and transport. Nanomaterials present researchers with what Wiesner described as “pervasive high levels of uncertainty” and issues of uniformity as investigators strive to understand how their novel qualities of size, shape, adsorptive surface area, aggregation kinetics and other qualities — even the way they are manufactured and integrated into finished products — may impact their behavior and, ultimately, any effect they could have on human health.

“We’re very interested in how particles approach each other, contact and stick,” Wiesner continued. “It affects the rates of rate of aggregation, it affects the rate of settling, and it also affects, as it turns out, the reactivity.” Aggregation patterns, Wiesner reasoned, are likely responsible for the apparent paradox involving reactive oxygen species production by tightly packed aggregates of molecules of a compound and single molecules of the same compound.

Nanomaterials, Wiesner emphasized several times in the talk, present researchers with many variables that need to be resolved before the apparent safety of the materials in the environment, observed so far, can be properly assessed. “When we start out with the materials in the bottle and put them in nature,” Wiesner concluded, “the characteristics of those materials are going to be very different than they would have been initially, and we need to account for that difference when we do eco-tox studies.”

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Upcoming Distinguished Lecture Features Michael Mendelsohn

By Eddy Ball

NIEHS will welcome the next speaker in its 2008-2009 Distinguished Lecture Series on February 10 at 11:00 a.m. in Rodbell Auditorium. Michael Mendelsohn, M.D., will present a seminar on “Estrogen Receptor Action in the Cardiovascular System” hosted by NIEHS Principal Investigator and Chief of the Receptor Biology Group Ken Korach, Ph.D.

[Mendelsohn](#) is a professor of Molecular Cardiology and Medicine at the Tufts University School of Medicine and executive director of the [Molecular Cardiology Research Institute](#) at the New England Medical Center.

According to Mendelsohn, the seminar will review and update the large body of current data regarding the specific roles of estrogen receptor



Distinguished Lecturer Mike Mendelsohn in his lab at Tufts University (Photo courtesy of Mike Mendelsohn and Tufts University)

(ER) in cardiovascular physiology and disease. He plans to discuss biological explanations for the Women's Health Initiative (WHI) -generated controversy regarding the role of hormone replacement therapy (HRT) in cardioprotection, as well as review newer clinical evidence that supports beneficial cardiovascular effects of HRT for menopausal women. Mendelsohn will discuss that evidence in the context of basic science and animal studies that define differences in the underlying vascular biology between younger and older menopausal women, addressing the clinical importance of the timing of HRT initiation — the “Timing Hypothesis.”

The presentation will also cover several newer signaling concepts in sex steroid hormone receptor action with important implications for cardiovascular physiology and disease. Mendelsohn will report on new experiments using mice in which ER are selectively deleted from smooth muscle cells to study the role of ER in vascular physiology.

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Cidlowski to Speak in Duke Immunology Seminar Series

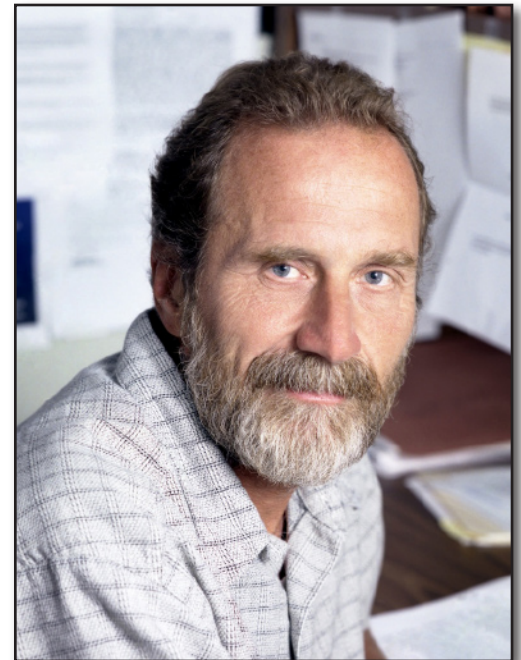
By Eddy Ball

NIEHS Principal Investigator John Cidlowski, Ph.D., will lecture on February 17 at 4:00 p.m. in 143 Jones Building on the Duke University campus. His talk, “The Secret Lives of Glucocorticoid Receptors,” is part of the Duke University Medical Center Department of Immunology Seminar Series.

Cidlowski heads the Molecular Endocrinology Group within the Laboratory of Signal Transduction (LST), and is chief of the LST. His major research interests are glucocorticoid receptors and their actions on inflammatory response triggered by environmental stress via steroid hormone action and the regulation of apoptosis in normal and neoplastic cells. He has published more than 250 peer-reviewed articles in leading biomedical journals, as well as several book chapters. Cidlowski served as a professor in the Physiology, Nutrition and Biochemistry departments at the University of North Carolina at Chapel Hill before joining the NIEHS in 1995.

In June 2008, Cidlowski was presented with the 2008 Edwin B. Astwood Award at the Endocrine Society's 90th Annual Meeting in San Francisco.

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*Edwin B. Astwood Award winner John Cidlowski
(Photo courtesy of Steve McCaw)*

This Month in EHP

By Eddy Ball

The February 2009 issue of *Environmental Health Perspectives* is now available on-line, highlighting issues surrounding global warming/climate change, endocrine disruptors and the health effects of air pollution.

- [Carbon Offsets: Growing Pains in a Growing Market](#) — describing the concept of the carbon offsets system and examining some of the implementation and regulation questions surrounding it
- [Biochar: Carbon Mitigation from the Ground Up](#) — looking at the possibilities of adding biomass charcoal (biochar) to soil to capture carbon and improve the quality of the air we breathe
- [Chemoresistance by Bisphenol A](#) — presenting evidence that BPA at environmentally relevant doses appears to reduce the efficacy of chemotherapeutic agents in treating breast cancer
- [Phthalates in Medications](#) — exploring issues surrounding the exposure to phthalates in the polymer coating of some oral medications and concerns about the effects on pregnant women and children
- [Modification by Influenza on Air Pollution Effects](#) — evaluating how influenza could modify the estimated risks of respiratory disease outcomes from exposure to air pollutants, particularly ozone



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Extramural Update

Partnerships for Environmental Public Health Announces New Funding Opportunity

After fifteen months of work dedicated to the establishing the new Partnerships for Environmental Public Health (PEPH) program, the Division of Extramural Research and Training (DERT) at NIEHS announced the first Request for Applications (RFA) titled “Research to Action: Assessing and Addressing Community Exposures to Environmental Contaminants.”

DERT staff developed the RFA after considering the comments and recommendations received from the extramural community through a [Request for Information \(RFI\)](#) and an informational [workshop](#) sponsored by the DERT in 2008. In particular, this RFA places a strong emphasis on research leading to action and the inclusion of community partners at all stages of the project, from co-development of research questions through implementation of the public health action plan.

NIEHS, in partnership with the National Institute of Occupational Health and Safety (NIOSH), designed this “Research to Action” RFA to support grant applications that will accomplish three central activities — collect data, translate findings into public health action, and evaluate processes and outcomes. Applicants

are encouraged to focus on emerging threats to communities and workers, environmental exposures that disproportionately burden low-income or minority communities, and exposure-related diseases that are of the greatest concern to the public.

The research efforts in these areas will be used to fill vital information gaps needed for environmental public health action, such as education, outreach, prevention or intervention programs. Additionally, the application must include an evaluation of the project's processes, including interactions between research and community partners, development and dissemination of educational materials, and outcomes, such as usefulness of materials produced and reductions in exposure to hazardous agents.

Applicants responding to this RFA may request up to \$225,000 in direct costs per year for up to four years. The NIEHS intends to commit \$2 million in FY2009 to fund five to seven new grants, and NIOSH intends to commit \$500,000 in FY2009 to fund one or two new grants. All applications are due by April 1, 2009. Awards will be made in September 2009. A complete copy of the [RFA](#) is available on the NIH Guide website.

All potential applicants to this RFA are encouraged to attend a pre-application technical assistance “virtual” meeting on February 3, 2009 from 1-3:00 p.m. Eastern Standard Time. The purpose of the informational meeting is to provide technical assistance on and answer questions related to the preparation of applications. Additional information is available online at <http://tools.niehs.nih.gov/conferences/dert/rfa/index.cfm>. Please note that pre-registration is required.

The “Research to Action” RFA is just the beginning of many new funding opportunities and activities planned under the PEPH program, which promises to be a vital component of the NIEHS’ commitment to reducing the burden of human disease and disability attributable to environmental exposures and improving human health. The extramural community is encouraged to keep an eye out for several other exciting PEPH developments in 2009. In February 2009, the PEPH program will launch a new website that will provide the public with quick access to information on PEPH, as well as NIEHS-sponsored and NIH-wide programs that fall within the mission of PEPH. The website will also provide a consolidated list of quick links to potential PEPH-related funding and training opportunities.

Contact: [Caroline H. Dilworth, Ph.D.](#)



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Extramural Papers of the Month

By Jerry Phelps

Selenium May Prevent High-Risk Bladder Cancer

NIEHS grantees at Dartmouth Medical School report in a new study that selenium may help prevent high-risk bladder cancer. The study found that women, moderate smokers and people with p53-positive tumors showed significant reductions in bladder cancer with higher selenium intake.

In the U.S., bladder cancer is the fourth most common cancer among men and the twelfth most common among women with approximately 67,000 cases being diagnosed each year. About 13,000 deaths are expected this year from bladder cancer. Bladder cancer develops through different pathways, but one of the major paths is through alterations in the *p53* gene. These cancers are associated with more advanced disease.

The study involved 857 people with newly diagnosed bladder cancer. Selenium intake was measured by analyzing toenail clippings. Cancer risk was reduced 30 to 50 percent in the three groups as selenium intake increased.

The exact mechanism by which selenium inhibits carcinogenesis is unknown, but it may occur through several mechanisms, including reducing oxidative stress and inflammation, enhanced immune responses and activation of DNA repair genes. The results of this study may provide clues on how to prevent tumors from developing and potentially lead to new chemotherapeutic agents.

Citation: Wallace K, Kelsey KT, Schned A, Morris JS, Andrew AS, Karagas MR. 2009. Selenium and risk of bladder cancer: a population-based case-control study. *Cancer Prev Res (Phila Pa)* 2(1):70-73.

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Gene Packaging is Important in Cancer

New NIEHS-supported research suggests that the packaging of genes may be as important as the genes themselves when it comes to the development and treatment of cancer. The findings point to the three dimensional chromatin packaging around genes formed by tight loops of polycomb group (PcG) proteins. Chromatin packaging is a complex combination of DNA and proteins that compresses the DNA to fit inside the cell nucleus and keep genes in a low expression state.

The researchers compared embryonic cells to adult colon cancer cells. The gene studied, *GATA-4*, is packaged by PcG proteins. In the embryonic cells the gene is in a low expression state and has no methylation. When the gene received signals for the cells to mature, the protein structures were disrupted and the gene was highly expressed. However, when the same gene was methylated, as is the case in the colon cancer cells, the PcG protein packaging loops were tighter and there was no gene expression. When the researchers removed the methylation, the cancer cells behaved similarly to the embryonic cells.

When the normal processes are disrupted and some genes are improperly methylated, important tumor suppressing cell functions can shut down. This research suggests that for therapies that remove abnormal DNA methylation from genes to be fully effective, researchers may need to search for agents that disrupt the PcG protein loops.

Citation: [Tiwari VK](#), [McGarvey KM](#), [Licchesi JD](#), [Ohm JE](#), [Herman JG](#), [Schübeler D](#), [Baylin SB](#). 2008. PcG proteins, DNA methylation, and gene repression by chromatin looping. *PLoS Biol* 6(12):2911-2927.

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Dopamine Transmission Impaired by Manganese

NIEHS grantees report that manganese exposure inhibits dopamine neurotransmission from the substantia nigra region of the brain, leading to motor activity impairments resembling those seen in Parkinson's disease. These results follow on previous studies from their laboratory using cynomolgus macaques. Previous research has shown that these monkeys show cognitive and fine motor deficits in response to manganese exposure.

The debilitating neurological condition manganism results from chronic high-dose exposure to the essential trace mineral manganese. Manganese-induced parkinsonism most often results from high exposure in industrial settings related to steel production; however, other sources include the impairment of manganese excretion in some liver diseases, high doses of manganese from parenteral nutrition, illicit psychostimulant drugs and, possibly, ambient concentrations generated from gasoline containing the additive methylcyclopentadienyl manganese tricarbonyl.

The monkeys were treated weekly with manganese doses ranging from 3.3-10 milligrams per kilogram body weight from seven up to 59 weeks. They received PET scans prior to the beginning of dosing and at one or two time points during the exposure. The researchers found that amphetamine-induced dopamine release was markedly reduced in the manganese-exposed animals. They concluded that the manganese exposure is responsible for the motor deficits documented in the monkeys. These findings may have implications for the prevention and treatment of symptoms of parkinsonism.

Citation: [Guilarte TR](#), [Burton NC](#), [McGlothan JL](#), [Verina T](#), [Zhou Y](#), [Alexander M](#), [Pham L](#), [Griswold M](#), [Wong DF](#), [Syversen T](#), [Schneider JS](#). 2008. Impairment of nigrostriatal dopamine neurotransmission by manganese is mediated by pre-synaptic mechanism(s): implications to manganese-induced parkinsonism. *J Neurochem* (5):1236-1247.

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Dioxin Disrupts Prostate Development

Researchers at the University of Wisconsin in Madison have determined the mechanism by which dioxin disrupts prostate gland formation in laboratory mice. They found that when dioxin is administered maternally at days 15 and 16 of gestation, the chemical inhibits the formation of certain prostate buds in two different regions (ventral and dorsolateral).

Members of this research team have previously shown that dioxin exposure during the fetal and neonatal periods inhibits prostate budding, thereby reducing the number of prostate ducts and causing a reduction in prostate size. There is also a growing body of scientific evidence that dioxin exposure in humans causes prostate cancer.

Experimental results show that hyperactivation of the aryl hydrocarbon receptor signaling pathway changes the patterning of the fetal urogenital sinus, disrupting where prostate buds develop and where prostate lobes are formed. The current study presents a new paradigm of how *in utero* dioxin exposure disrupts prostate formation, suggesting this same mechanism may in part explain how dioxin impairs the development of other organs and tissues.

Citation: [Vezina CM, Allgeier SH, Moore RW, Lin TM, Bemis JC, Hardin HA, Gasiewicz TA, Peterson RE. 2008. Dioxin causes ventral prostate agenesis by disrupting dorsoventral patterning in developing mouse prostate. Toxicol Sci 106\(2\):488-96.](#)

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

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Intramural Papers of the Month

By Robin Arnette

Researchers Find a Novel Target for Glycogen Synthase Kinase 3Beta Phosphorylation

Scientists at NIEHS have determined that glycogen synthase kinase 3 β (GSK-3 β) phosphorylates the human glucocorticoid receptor (GR) in a hormone-dependent manner. This discovery represents a new target for GSK-3 β phosphorylation and has a bearing on a myriad of biological functions, everything from cell growth and metabolism to apoptosis or cell death.

Using Western blot analysis, immunoprecipitations, immunofluorescence, microarray analysis and PCR, the researchers determined that following the stimulation of glucocorticoids — steroid hormones that affect the metabolism of carbohydrates and inhibit the process of inflammation — GSK-3 β phosphorylates GR on Ser404. The team also found that this event altered the ability of GR to function as a transcription factor. However, cells that lacked the potential for GR-Ser404 phosphorylation increased their chances of undergoing apoptosis.

These findings provide a novel convergence point between GSK-3 β and the GR pathway and suggest that cellular conditions that result in altered GSK-3 β activity influence how cells respond to hormone stimulation.

Citation: [Gallagher-Beckley AJ, Williams JG, Collins JB, Cidlowski JA](#). 2008. Glycogen synthase kinase 3 β -mediated serine phosphorylation of the human glucocorticoid receptor redirects gene expression profiles. *Mol Cell Biol* 28(24):7309-7322.

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The Histone Deacetylase Inhibitor Trichostatin A Upregulates NAG-1

Researchers from NIEHS and Tottori University in Japan have found that the putative tumor suppressor, nonsteroidal anti-inflammatory drug-activated gene (NAG-1), is induced by the histone deacetylase (HDAC) inhibitor trichostatin A (TSA). Since HDAC inhibitors are possible therapeutic agents for treating glioblastoma, a common central nervous system tumor, the findings may lead to the use of other HDAC inhibitors in treating malignant brain tumors.

NAG-1 is a tumor suppressor gene that responds to drug treatment by increasing its expression, so the team tested the drugs TSA and the DNA demethylating agent 5-aza-dC to see if they would alter NAG-1 expression in human T98G human glioblastoma cells. 5-aza-dC did not increase NAG-1 expression, but TSA up-regulated NAG-1 and acted synergistically with 5-aza-dC to induce NAG-1 expression. The team also determined that the induction of NAG-1 by TSA involved not only transcriptional regulation via Sp-1 and Egr-1, but also post-transcriptional regulation.

Citation: [Yoshioka H, Kamitani H, Watanabe T, Eling TE](#). 2008. Nonsteroidal anti-inflammatory drug-activated gene (NAG-1/GDF15) expression is increased by the histone deacetylase inhibitor trichostatin A. *J Biol Chem* 283(48):33129-33137.

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A Role for CYP2J5 in Blood Pressure Regulation via an Estrogen-Dependent Mechanism

Female mice that lacked the *Cyp2j5* gene (*Cyp2j5*^{-/-}) displayed increased blood pressure and vascular responsiveness compared to wild-type female mice. In addition *Cyp2j5*^{-/-} mice exhibited reduced 17 β -estradiol levels, and estrogen replacement restored normal blood pressure and vascular responsiveness. These results provide the first direct evidence of a role for *Cyp2j* subfamily cytochrome P450s in blood pressure regulation and indicate that the *Cyp2j5*^{-/-} vascular phenotype is estrogen responsive. The work represents a collaborative effort from researchers at several institutions including NIEHS.

Mouse CYP2J5 is abundant in the kidney where its eicosanoid products, the *cis*-epoxyeicosatrienoic acids (EETs), modulate sodium transport and vascular tone. The research team wanted to determine the role of CYP2J5 in the kidney, so members generated *Cyp2j5*^{-/-} mice. Although the investigators did not observe an effect on EET biosynthesis, they did observe altered estrogen levels and increased blood pressure in the female mutant mice.

Other labs have reported that the disruption of the *Cyp4a10* and *Cyp4a14* genes in mice leads to increased blood pressure and that a polymorphism in the *CYP4A11* gene is associated with hypertension in humans. Other groups have also found that sex hormones are involved in the pathogenesis of hypertension in rodents and humans. Further studies with *Cyp2j5*^{-/-} mice may lead to a better understanding of the complex relationships between blood pressure, sex hormones and renal eicosanoids.

Citation: Athirakul K, Bradbury JA, Graves LP, DeGraff LM, Ma J, Zhao Y, Couse JF, Quigley R, Harder DR, Zhao X, Imig JD, Pedersen TL, Newman JW, Hammock BD, Conley AJ, Korach KS, Coffman TM, Zeldin DC. 2008. Increased blood pressure in mice lacking cytochrome P450 2J5. *FASEB J* 22(12):4096-4108.

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Computational Studies of the Catalytic Mechanism of Human DNA Polymerase Lambda

Using the pre-catalytic complex of DNA polymerase λ (Pol λ) as the basis of their studies, researchers at NIEHS determined the molecule's catalytic mechanism using either magnesium (Mg^{2+}) or manganese (Mn^{2+}) as the divalent metals in the active site.

The team employed quantum mechanical/molecular mechanical (QM/MM) methods and performed two sets of calculations with each metal. This work is the first to computationally compare the two-metal ion catalytic mechanism of a DNA polymerase with either Mg^{2+} or Mn^{2+} in the active site.

DNA polymerases are responsible for DNA replication and repair. The chemical step catalyzed by these enzymes involves a nucleophilic attack to incorporate the incoming nucleotide onto the DNA primer. Several studies have revealed that human Pol λ , a member of the X family of polymerases, can use either Mn^{2+} or Mg^{2+} to catalyze this reaction.

The investigators concluded that for both metals, the catalytic reaction proceeds through a two-step mechanism where the 3'-OH of the primer sugar ring is deprotonated in the active site by Asp490, followed by the incorporation of the incoming nucleotide to the primer DNA chain. They also found that several residues surrounding the active site appear to be important for catalysis. In addition, they showed that some of these residues are conserved among X family polymerases.

Citation: Cisneros GA, Perera L, García-Díaz M, Bebenek K, Kunkel TA, Pedersen LG. 2008. Catalytic mechanism of human DNA polymerase lambda with Mg^{2+} and Mn^{2+} from *ab initio* quantum mechanical/molecular mechanical studies. *DNA Repair (Amst)* 7(11):1824-1834.

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Inside the Institute

Wilson to Focus on Research Full Time

By Eddy Ball

Samuel H. Wilson, M.D., the long-time Deputy Director and recent Acting Director of the National Institute of Environmental Health Sciences (NIEHS) and the National Toxicology Program (NTP), announced his decision to step away from his administrative roles at the Institute. In a message to NIEHS employees, Wilson said that he plans to devote more time to his research as a principal investigator and chief of the NIEHS Laboratory of Structural Biology DNA Repair and Nucleic Acid Enzymology Group — a decision made much easier, he said, because of “my complete confidence in the leadership of the incoming director, Dr. Linda Birnbaum.”

Wilson, who joined NIEHS in 1996 as deputy director under former Director Kenneth Olden, Ph.D., assumed his duties as acting head of NIEHS in August 2007, succeeding then Director David Schwartz, M.D. In that role, he provided continuity for the Institute through the transition until Birnbaum took office in January 2009.

Wilson leaves with a legacy of supporting NIEHS programs in environmental genomics and environmental public health. During his tenure, Wilson and his leadership team underscored NIEHS support for basic research in the Institute’s Division of Intramural Research and strengthened ties with the NIEHS extramural community through a series of site visits to grantees throughout the United States. He increased the NIEHS commitment to its journal, *Environmental Health Perspectives (EHP)*, which recruited a new editor-in-chief during the transition, and reaffirmed institutional support for the environmental justice and community-based participatory research communities.

During the winter of 2007-2008, he and his team increased NIEHS participation in global environmental health and climate change partnerships at the national and international levels. In December 2007, he represented NIEHS leadership at the 20th anniversary of the Superfund Basic Research Program.

With his encouragement, the NIEHS Division of Extramural Research and Training initiated the innovative Partnership for Environmental Public Health program in 2008. Wilson joined leaders of NTP in November 2008 to celebrate the program’s 30 years of accomplishments.

When Wilson became acting director, he set the tone for his tenure by telling NIEHS employees, “Just call me Sam,” and was known within the Institute for his candor and accessibility. He was a vocal advocate for quality career development opportunities for fellows and junior investigators, as well as a proactive supporter of diversity and accommodation for employees with disabilities.



(Photo courtesy of Steve McCaw)

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NIEHS Scientists Get Tips on Giving Better Presentations

By Robin Mackar

Developing and delivering a compelling PowerPoint presentation can be a challenge, but for the 24 scientists who participated in a two-day training class coordinated by the NIEHS Office of Communications and Public Liaison (OCPL), that task may now be a little easier.

OCPL teamed with the National Toxicology Program (NTP) to sponsor presentation skills training sessions for two groups of NIEHS scientists and administrators in January. The sessions were specifically designed to help NIEHS staff improve their presentation skills. After initial sessions on January 15 and 23, the participants assembled back in Rodbell Auditorium a week later to test their new skills. Each participant gave a ten minute presentation that was critiqued by the trainer and other attendees. The training was led by Rick Grandinetti of VisionPlanning, Inc. in Morrisville, N.C.

Scientists from the Divisions of Intramural Research, Extramural Research and Training, as well as the NTP, participated.

“The course provided many useful tips to improve both slide content and the delivery of the presentation,” said training participant Matt Stout, Ph.D., of the NTP. “However, what truly set this course apart was the feedback on a live presentation from both colleagues and the instructor.”

According to OCPL Director Christine Flowers, her office will continue to provide training for a variety of communications skills, including classes on doing media interviews, writing and public speaking.

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

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The first of the two-day training sessions included an overview on speech and presentation skills. The sessions are geared to engage people in the audience such as Heather Henry, Ph.D., center, and NTP Postdoctoral Fellow Chad Blystone, Ph.D. (Photo courtesy of Steve McCaw)



During the personalized coaching sessions on day two, Blystone was dressed for the occasion as he presented and then received feedback from the trainer and fellow attendees. (Photo courtesy of Steve McCaw)



During the sessions, Grandinetti, above, discussed ways to integrate effective audiovisual aids into presentations. The key, he said, is to use slides to support the presentation without repeating word for word what appears on the screen.

NIEHS Staffers Bring Help to Durham Homeless

By Eddy Ball

The bitter cold on Friday January 16 failed to hamper the generosity of a group of NIEHS employees who transported donated food to a shelter for the homeless in Durham, NC. The effort was spearheaded by employees in the NIEHS Division of Extramural Research and Training (DERT) via the Community Builders Committee and members of the Research Triangle Chapter of [Blacks in Government \(BIG\)](#), an inter-agency service group, who collected food over the Christmas and New Year's holidays.

Friday turned out to be the coldest day so far this year in central North Carolina with lows in the teens and single digits. It was the kind of day that inspires shelters to fly a white flag to indicate that everyone who needs a warm place to sleep will be accommodated. With temperatures that low, there is a real danger that people sleeping outside could suffer hypothermia, frostbite and even death. With the white flag flying, shelters also experience an increased need for food.

“We [in DERT] wanted to do something for the holidays,” said Worker Education and Training Program Administrator Sharon Beard. “We took care of everything over here in Keystone [the satellite facility where more than 300 NIEHS employees have offices], and BIG handled collections on the main campus.”

Beard joined NIEHS Project Officer and BIG President Veronica Godfrey, DERT Health Science Administrator Caroline Dilworth, Ph.D., and Superfund Basic Research Program Program Administrator Heather Henry, Ph.D., in the lobby of the Keystone Building. There they loaded the food and left for the [Durham Rescue Mission](#), which has seen a dramatic rise in demand for services through its Operation Warm Shelter with the downturn in the economy.

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Left to right, Godfrey, Dilworth and Beard posed with some of the cans and boxes of food collected during the holiday drive. (Photo courtesy of Steve McCaw)



Henry, center, joined Godfrey and Dilworth as they braved sub-freezing temperatures to load the food for the drive to downtown Durham. (Photo courtesy of Steve McCaw)



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