

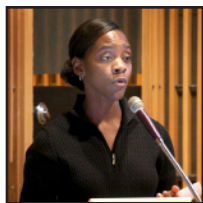


Environmental Factor

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February 2008

NIEHS Spotlight



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January 17 in Rodbell Auditorium to welcome new — and several old — trainees. ...[read more](#)



Scientists Link Health and Climate Change at National Meeting

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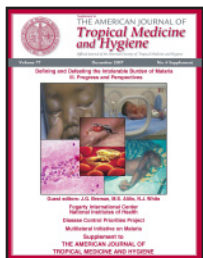


With IRB OK, Researchers Launch New Breast Cancer Study

Investigators Clarice Weinberg, Ph.D. and Dale Sandler, Ph.D., had reason to celebrate on January 18 when they

learned that the NIEHS Institutional Review Board (IRB) had given final approval for launching their new study of breast cancer, known as the Two Sister Study.

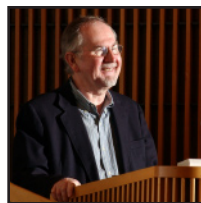
....[read more](#)



Institute Helps Disseminate Malaria Publication

NIEHS was one of the supporters of a 340-page supplement on malaria published in the December 2007 issue of the *American Journal of Tropical Medicine and Hygiene*. ...[read more](#)

Science Notebook



Inflammasome and Infection

In Rodbell Auditorium on January 8, 2008, NIEHS welcomed Richard A. Flavell, Ph.D., as part of the continuing 2007–2008 NIEHS Distinguished Lecture series. ...[read more](#)



Evolution of Human Genome's 'Guardian' Network

Human evolution has created enhancements in key genes connected to the p53 regulatory network -- the so-called guardian of

the genome -- that boost the network's safeguards against DNA damage that could cause cancer or a variety of genetic diseases, according to an international team of scientists led by the National Institute of Environmental Health Sciences (NIEHS) that included Cincinnati Children's Hospital Medical Center. ...[read more](#)



Superfund Study of Toxins in China's Freshwater Ecosystem

Scientists from Dartmouth College, Lakeland College, and the Chinese Academy of Sciences in Beijing

investigated the bioaccumulation and trophic transfer of the toxic metals, mercury and arsenic, in Lake Baiyangdian, China.[read more](#)

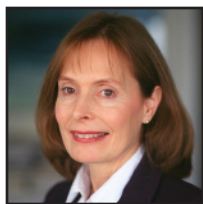
NIEHS Spotlight



Senior Trainee to Establish Free Radical Lab

NIEHS research fellow Dario Ramirez, Ph.D., leaves NIEHS in February to begin a new phase in his career and set up his own lab for his new job in

Oklahoma City, after working for seven years in the NIEHS Laboratory of Pharmacology and Chemistry (LPC). [...read more](#)



DISCOVER Grants Awarded

The National Institute of Environmental Health Sciences (NIEHS) announced awards totaling \$6.8 million for the first year of funding to three new research centers called DISCOVER centers.

[...read more](#)



Enhancing Oceans and Human Health Initiative

Four years after launching the Centers for Oceans and Human Health (COHH) collaboration with the National Science Foundation, NIEHS continues to expand

its strategic partnerships within the larger global oceans community. [....read more](#)



Julianne Malveaux Speaks at King Celebration

On Wednesday January 16, NIEHS employees celebrated the life and legacy of Dr. Martin Luther King, Jr., at a standing-room-only event held

at the neighboring Environmental Protection Agency (EPA) Main Auditorium. [...read more](#)



Durham Careers in Science Consortium Meets at NIEHS

Finding ways to augment science curriculum and activities — and consequently turn young people on to careers in science — is the goal of a diverse group of educators,

business people, scientists and community leaders who gathered at NIEHS January 14 for a meeting of Durham Careers in Science (DCIS). [....read more](#)

Science Notebook



Portier Outlines Strategy for HTS Pathway Analysis

The January 9 talk by NIEHS Associate Director Chris Portier, Ph.D., in Rodbell Auditorium was the first in a series of seminars sponsored by

the National Toxicology Program (NTP) Biomolecular Screening Branch. [...read more](#)



Upcoming Distinguished Lecture Features Mitchell Lazar

The 2007-2008 NIEHS Distinguished Lecture Series continues at 11:00 a.m. February 13 with a talk by Mitchell

Lazar, M.D., Ph.D., on “Nuclear Receptor Regulation of Metabolism.” Lazar’s talk will take place in Rodbell Auditorium and be hosted by Trevor Archer, Ph.D., chief of the NIEHS Laboratory of Molecular Carcinogenesis. [...read more](#)

Extramural Research

Extramural Update

On September 4, 2007, NIEHS extramural and intramural staff met with twelve international air pollution research experts in Mexico City to discuss the breadth and depth of different air pollution studies around the world, and to assess the feasibility of comparing and pooling data to better understand the diverse clinical responses and genetic susceptibility to exposure to air pollution across different populations. [...read more](#)

Inside the Institute



An Outside Look at 530 Davis Drive

For the 350 or so NIEHS employees and contractors who work in the satellite office spaces at East Campus and Nottingham Hall, the final months of

2008 will mean making a move into consolidated office space at 530 Davis Drive in Keystone. ...[read more](#)



Black History Month Events

Campus and area organizers have finalized arrangements for three events during February to celebrate Black History Month — a yearly acknowledgement of the struggles and

accomplishments of African Americans. ...[read more](#)

Family Health Transitions Seminar Series Begins February 6

The NIEHS Office of Management and the Disability Advocacy Committee are sponsoring a series of six seminars on family health transitions topics. The presentations will take place on Wednesdays during February and March in the Executive Conference Room and will feature local experts with non-profits and businesses.[read more](#)



White Tigers Land Again in Rodbell

Rodbell Auditorium was the scene once more of youngsters flying through the air, boards cracking into pieces from well-placed kicks

and grunts punctuated by the thud of landing feet as students from the White Tiger Taekwondo School in Cary took over the stage January 18 during their third visit to the Institute.[read more](#)

NIEHS Papers of the Year 2007

NIEHS investigators and grantees published nearly 2,800 peer-reviewed scientific studies in 2007. Fifteen studies are highlighted here with findings that range from new insights into basic mechanisms to the demonstration of potentially useful applications of research in the clinical setting:

- [IL-6 and Gender Differences in Liver Cancer Rates](#)
- [Polymerase Stalling and Transcriptional Regulation](#)
- [S-nitrosothiols: Possibilities in Fighting Asthma and Heart Disease](#)
- [Breast Enlargement in Prepubertal Boys](#)
- [Mutant Astrocytes Play a Role in the Degeneration of Motor Neurons in Amyotrophic Lateral Sclerosis \(ALS\)](#)
- [Unique Substrate Specificity of DNA Polymerase Mu](#)
- [Predictive Gene Also Maintains Differentiation of Mammary Ductal Cells](#)
- [Genes in Blood Can Predict Harmful Levels of Acetaminophen](#)
- [Inhibition of RelB Synthesis by ER \$\alpha\$ Signalling Controls the Shift in Breast Cancer Cell Phenotypes](#)
- [RNA Direct Transfer of Genetic Information](#)
- [Supplementation Counteracts Bisphenol A-Induced Epigenetics Changes](#)
- [DNA Polymerase Epsilon and Leading Strand DNA Replication](#)
- [Study Links Gene Expression Changes in Babies to Arsenic Exposure](#)
- [Identification of a New Base Excision Repair Cofactor](#)
- [Parkinson-like Degenerative Changes Linked to Reduced Dopamine Storage](#)

Calendar of Upcoming Events

- **February 1** in Rodbell Auditorium, 9:00 – 10:00 — Frontiers of Environmental Sciences Lecture Series featuring Anna Maria Siega-Riz, Ph.D., speaking on “Maternal Obesity-The Number One Problem Facing Prenatal Care Providers In The New Millennium”
- **February 5 (Offsite Event)** at the Consumer Product Safety Commission Headquarters in Bethesda, Md., 1:00 – 5:00 — Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) Ten-Year Anniversary Symposium, Celebrating the Advancement of Public Health and Animal Welfare With Sound Science: Envisioning New Directions in Toxicology
- **February 13** in Rodbell Auditorium, 11:00 – 12:00 — Distinguished Lecture with Mitchell A. Lazar, M.D., Ph.D., speaking on “Nuclear Receptor Regulation of Metabolism”
- **February 15** in Rodbell Auditorium, 9:00 – 10:00 — Frontiers of Environmental Sciences Lecture Series with Jim Putney, Ph.D., topic TBD
- **February 19 – 21 (Offsite Event)** at the Doubletree Hotel, Tampa, Florida — Assessing Bioavailability as a Determinant of Pollutant Exposure: Building a Multidisciplinary Paradigm for the 21st Century and Beyond
- **February 20** in Rodbell Auditorium, 8:00 – 5:00 — NIEHS National Advisory Environmental Health Sciences Council Meeting
- **February 21** in Rodbell Auditorium, 10:00 – 11:00 — Laboratory of Molecular Genetics Seminar Series talk on “Genes, Environment and Chance: Their Role in Aging” by Tom Johnson, Ph.D.
- **February 22** in Rodbell Auditorium, 9:00 – 10:00 — Frontiers of Environmental Sciences Lecture Series featuring Mariano A. Garcia-Blanco, M.D., Ph.D., topic TBD
- **February 27-28** in Rodbell Auditorium, 8:30 – 5:00 — National Toxicology Program Board of Scientific Counselors Technical Reports Review Subcommittee Meeting
- **February 28 (Offsite Event)** at the Natcher Center in Bethesda, Md., 8:00 – 5:00 — Cells to Society: Overcoming Health Disparities
- **February 29** in Rodbell Auditorium, 9:00 – 10:00 — Frontiers of Environmental Sciences Lecture Series talk by Ruben Carbonell, Ph.D., topic TBD
- **March 4 – 6 (Offsite Event)** at the United States Geological Survey National Center in Reston, Virginia — Geological Society of America special meeting, “GeoHealth I: Building Bridges across the Geological and Health Sciences”
- View More Events: [NIEHS Public Calendar](#)

NIEHS Spotlight

NIEHS Welcomes Trainees

By Eddy Ball

As part of a continuous effort to improve postdoctoral training at NIEHS, the Institute held what organizers described as the first ever systematic NIEHS Trainee Orientation January 17 in Rodbell Auditorium to welcome new — and several old — trainees.

The event was chaired by Bertina Jones, Ph.D., chair of the NIEHS Trainees Assembly (NTA) Orientation Committee, and featured talks by NIEHS Acting Director Sam Wilson, M.D., and key personnel from the [NIEHS Office of Fellows Career Development \(OFCD\)](#), the NTA, which organized the program, and the [NIH Office of Intramural Training and Education \(OITE\)](#).

Speakers at the two-hour meeting covered topics that ranged from the philosophical and scientific, such as the mission of NIH/NIEHS and the “whole person” concept of training for fellows, to the mundane and practical, including the excused leave policy, use of the Junction web site and the specific logos required on all NIEHS presentations. Nearly 30 trainees were on hand for the event, which was also attended by Deputy Scientific Director Bill Schrader, Ph.D., and Associate Director for Management Marc Hollander.

By his presence as well as by his words, Wilson testified to the important role of post-baccalaureate and postdoctoral training at the Institute. He opened the orientation with an overview of NIEHS research initiatives and the Institute’s role in the NIH family of 27 Institutes and Centers — and where he sees the NIH/NIEHS moving in the future.

During the question-and-answer session, Wilson emphasized, “Postdocs are right at the top of the totem pole [at NIH/NIEHS]. You’re the future of the research enterprise in the country. Each principal investigator here depends on working with postdocs and fellows in the laboratory to be able to advance scientific projects.”



Bertina Jones was instrumental in organizing the meeting. She is shown here introducing Wilson. (Photo courtesy of Steve McCaw)



Along with learning more about the Institute and hearing Wilson express his commitment to quality training and development, trainees had a chance to enjoy his lighter side. (Photo courtesy of Steve McCaw)

A familiar face for many in the NIEHS trainee community, OITE Director Sharon Milgram described her talk as “the 20,000 foot answer to the question about what the NIH is doing to make sure that fellows are ready for a changing job market.” Noting that although the job market for fellows has changed dramatically, Milgram argued that in too many cases, training has not. “We need to train flexible, adaptable ‘whole people,’” she continued, “which is something that we have not done very well in the past.”

Milgram began her talk with a list of the kinds of skills “whole people” need to develop during their training in addition to competence in their field of science. “You have to develop personal skills, professional skills and career skills that allow you to seize opportunities quickly,” she argued.

Following Milgram were NTA leaders Jennifer Adair, Ph.D., Co-chair Rose Ramos, Ph.D., and Chair Anastasia Wise, OFCD Acting Director Dianne Klotz, Ph.D., and OITE Deputy Director Pat Sokolove, Ph.D.

Adair introduced trainees to the resources link on the internal Junction web page and, with the help of Schrader, the process of getting approval for publication of abstracts and papers. In her segment, Klotz described the series of workshops offered to trainees each year and discussed the three new workshops scheduled for 2008: the mentoring program with the Summers of Discover program, leadership training and laboratory management training.

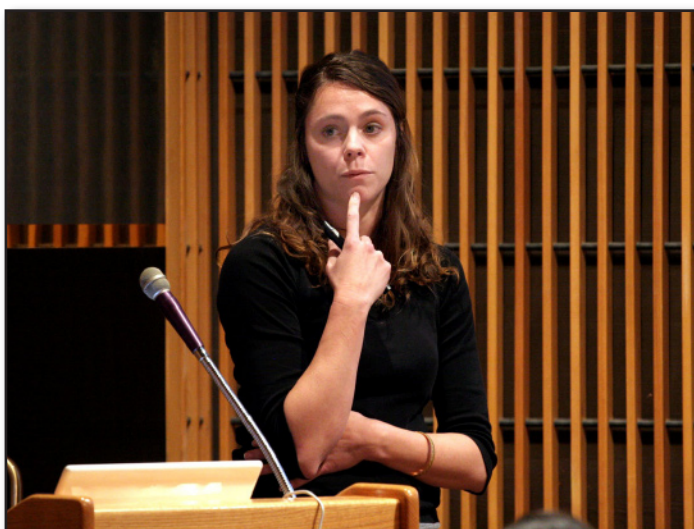
Sokolove, who spoke on “Administrative Information for Fellows,” showed the audience how to access the NIH Policy Manual and directed the trainees to sites that explain the differences among the three most common types of appointments, differences that affect how taxes are handled and that may impact future fellowship appointments.

Ramos and Wise were the final speakers at the event, urging the audience to participate in the organizations that represent them locally and nationally. As NIEHS liaison to the [National Postdoctoral Association \(NPA\)](#), Ramos emphasized the benefits of free membership in the NPA, an advocacy group with a number of important resources for trainees and graduate students. Wise encouraged trainees to become active in the NTA, which holds workshops and social events and sponsors the annual Biochemical Career Fair each spring.

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“People in Bethesda complain that my favorite group of fellows is here,” Milgram told the trainees. (Photo courtesy of Steve McCaw)



Adair pondered a question from a new trainee about support organizations and services linked to the NIEHS Junction web page. (Photo courtesy of Steve McCaw)

Scientists Link Health and Climate Change at National Meeting

By Eddy Ball

On January 16 the National Council for Science and the Environment convened its the Climate Change: Science and Solutions conference in Washington, D.C. The NIEHS was a sponsor for the meeting and had representatives on hand as participants (see text box). Three of the Institute’s scientists from the Laboratory of Molecular Toxicology were also there to present NIEHS-funded research at the poster session and contribute a public health perspective to the proceedings.

At the conference, fellows Julia Gohlke, Ph.D., and Melissa Chan, Ph.D., joined co-author and NIEHS Director of the Office of Risk Assessment Research Chris Portier, Ph.D., for the presentation of a poster abstract titled “A Systems Approach for Bridging the Gap between Human Health Research and Climate Change Research.” Their work addressed the emerging theme of human health and well being impacts of climate change and furthered one of the major goals of the conference — guiding and fostering multi-disciplinary research.

As lead author Gohlke explained, “Current discussions of climate change emphasize the need to reduce greenhouse gases based on rising sea levels and increased temperatures, yet the full global public health impacts of these climatic shifts are rarely considered. Our research is intended to demonstrate a better informed, holistic approach to risk assessment.”

What Gohlke, Chan and Portier presented were findings based on the systems approach that is increasingly a part of environmental health sciences research. The systems approach assumes a whole-organism, or in this case a global perspective and attempts to define the interactions within a network. The systems approach is especially suited to the integration of different disciplines and is typified by extensive laboratory and field measurement, data mining and modeling.

In its abstract, the NIEHS team argued for revising the conventional approach to human health research, which emphasizes molecular and cellular model systems, genetic determinants and therapeutic solutions to disease. They proposed expanding the model explicitly to include all environmental determinants — social, ecosystem and physical factors — in an assessment of risk. In the case of climate change, this expanded model would include health issues beyond heat- and cold-related mortality, such as social disruption due to water and food security problems, changing crop yields and changing ranges of vectors for infectious disease.



NIEHS Fellow and lead author Julia Gohlke. (Photo courtesy of Steve McCaw)



Visiting Fellow Melissa Chan, co-author of the study (Photo courtesy of Steve McCaw)

In a meta-analysis of data from the World Health Organization, the Intergovernmental Panel on Climate Change and the European Commission's ExternE Project, the team compared estimated mortality attributed to various energy sources, such as oil, which has the greatest impact on climate change, coal, which is linked to 90 percent of mortality associated with electricity-generation, and biomass, the cooking fuel widely used in developing countries and linked to respiratory diseases.

According to the abstract, however desirable reducing oil and coal emissions might be for long-term global health, the continued use of traditional biomass poses an even greater short-term risk to human health. If traditional biomass were replaced with coal-fired power plants, the increase of approximately 96,000 deaths associated with outdoor pollution and climate change annually would be substantially offset by the elimination of the 1,497,000 deaths each year attributed to use of traditional biomass, primarily in indoor cooking — a net savings of 1.4 million lives.

The researchers emphasized, however, that the long-term health impacts of climate change are likely to increase dramatically if no mitigation strategy is employed.

The researchers argued that a global systems perspective is needed for a balanced assessment of risk related to environmental threats. In contrast to previous energy policies developed without consideration of health impacts, the scientists concluded that “health endpoints in a social as well as ecological context must be considered as energy policies are developed to mitigate the effects of climate change.”

Increasing the NIEHS Presence in Efforts to Address Climate Change

Along with a poster presentation at the Climate Change: Science and Solutions Conference, NIEHS Associate Director Sharon Hrynkow, Ph.D., was on hand to represent the Institute with potential partners in efforts to address climate change. Hrynkow, who is the former acting director of the Fogarty International Center, is a key player in NIEHS global health initiatives and a vocal advocate of addressing social issues, including gender, in environmental health sciences research and programs. She has been assigned by Acting Director Sam Wilson, M.D., to serve as the Institute's point person on issues related to global warming and climate change.

According to Hrynkow, this year the Institute joined six other federal agencies in helping to sponsor the conference. “NIEHS is taking stock of its current programs in the climate change arena,” she explained. “This conference afforded us a critical opportunity to talk about some of our current work and to gain new insights and partners as we consider the next best steps on the climate change issue.”

Bethesda-based NIEHS Program Analyst Mary Gant was a member of the 2008 Conference Advisory Committee and moderated a session on Climate Change and Public Health on January 17. The public health experts at that session reflected on the critical need to mitigate the impact of adverse weather events and other sequelae of climate change and suggested ways of adapting to the negative implications of climate change.

Also representing NIEHS at the meeting was Allen Dearry, Ph.D., associate director, Division of Research Coordination, Planning and Translation.



Mary Gant is shown at the December 6 National Toxicology Program Board of Scientific Counselors' meeting. (Photo courtesy of Steve McCaw)



Sharon Hrynkow delivered a December 14 Frontiers of Environmental Sciences Lecture on gender, equity and environmental health, one of several research priorities that relate to global environmental health and climate change. (Photo courtesy of Steve McCaw)

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With IRB OK, Researchers Launch New Breast Cancer Study

By Eddy Ball

Investigators Clarice Weinberg, Ph.D. and Dale Sandler, Ph.D., had reason to celebrate on January 18 when they learned that the NIEHS Institutional Review Board (IRB) had given final approval for launching their new study of breast cancer, known as the Two Sister Study. Building on the large [Sister Study](#) cohort they have been recruiting since 2004, the investigators secured a commitment for three years of funding for the new study in 2007 and now plan to begin recruiting for the new study.

As Weinberg explained, “This study will use a family approach to elucidate the combined roles of genes and environmental factors in causing young-onset breast cancer, and in influencing the long-term prognosis and general health of women following treatment for breast cancer.” For this study, “young-onset” means age 50 or younger.

The study will attempt to recruit about 2,000 women with young-onset breast cancer who sisters of women already participating in the Sister Study. The investigators will invite any parents who are still living to contribute genetic data. It is being funded by a grant from [Susan G. Komen for the Cure](#), which is also a partnering organization for the Sister Study.

The investigation is being led by Weinberg, NIEHS Biostatistics Branch chief and principal investigator, and Sandler, Epidemiology Branch chief and co-investigator. Other investigators include Jack Taylor, M.D., Ph.D., Stephanie London, M.D., and Lisa DeRoo, Ph.D., of the Epidemiology Branch, and Min Shi, Ph.D., of the



Biostatistics Branch. As a companion to the larger Sister Study, the new study builds upon the strengths of the larger prospective study of the etiology of breast cancer but uses a family-based approach.

According to Weinberg, the subjects will include about 2,000 families with one daughter with breast cancer and another daughter without breast cancer, who meet enrollment criteria. Families to be selected will all have a daughter who developed breast cancer before the age of 50 and during the past three years and another daughter who is already in the Sister Study. Participants will provide saliva (for DNA) and dust samples, information about family and lifestyle, and details about their breast cancer diagnosis and treatment. The affected sisters will also be asked to give permission for release of medical records and tumor tissue blocks.



Principal Investigator Clarice Weinberg, left, and Co-investigator Dale Sandler (Photo courtesy of Steve McCaw)

Any of their living parents who are willing to participate will be asked to provide saliva samples for extraction of DNA. The plan is to genotype more than 1,500 markers on some 150 candidate genes and to use statistical methods to identify causative (or protective) genetic variants that tend to be over- or under-transmitted to offspring who later develop breast cancer. Maternal genetic effects and parent-of-origin effects can also be studied with this design, something the larger cohort study will not be able to do.

Looking to the future, Weinberg said, “I’m hoping that we’ll be able to afford to do a genome-wide association study for Two Sisters, where we look at maybe 500,000 SNP markers across the genome.” The archived DNA will serve as a resource for future tests of new candidate genes uncovered in ongoing whole genome scans and could potentially be employed in studies of gene-gene interactions and acquired epigenetic modifications.

Exposures related to risk will be identifiable from the comparison of the affected and unaffected sisters. The family structure will then provide a powerful basis for characterizing the combined effects of genetic and non-genetic risk factors.

The young-onset cases enrolled in the Two Sister Study will be merged with the incident cases diagnosed in the larger Sister Study during follow-up. Together, they will form a cohort of breast cancer survivors. The investigators hope to secure funding to follow these survivors for up to ten years to identify factors that influence prognosis and general health following treatment.

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Institute Helps Disseminate Malaria Publication

By Eddy Ball

NIEHS was one of the supporters of a 340-page supplement on malaria published in the December 2007 issue of the *American Journal of Tropical Medicine and Hygiene*. Funding from the NIEHS through a collaborative agreement with the Fogarty International Center (FIC) helped to make this important publication available free of cost to public health scientists and practitioners worldwide.

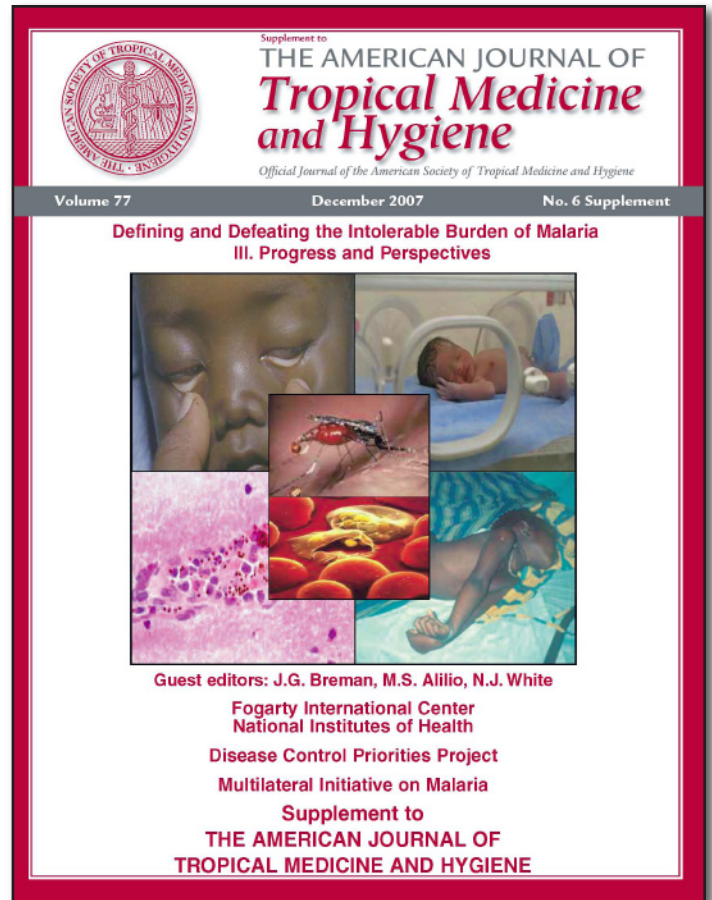
According to the [NIH press release](#) announcing the publication, “*Intolerable Burden of Malaria*” presents “new insights into the international burden of malaria and how the global community can best combat the disease,” including advances in genetic engineering, human and parasite genome sequencing, increasing access to affordable anti-malarial drugs and more specific categorization of infection types to improve treatment.

The authors are among the world’s leading research scientists, physicians and public health specialists working to combat the disease. The publication is the third in a series that began in 2001 and was edited by Joel Breman, M.D., senior scientific advisor at the FIC Division of International Epidemiology and Population Studies, Martin Alilio, Ph.D., formerly of FIC and now with the Academy for Educational Development, and Nicholas J. White, M.D., a distinguished professor of tropical medicine at Mahidol University in Bangkok, Thailand and Oxford University in England.

Serving as the secretariat for the publication, FIC was the NIH point organization for the project, which also received major funding from the National Institute of Allergy and Infectious Diseases, Centers for Disease Control and Prevention, and the Foundation for the National Institutes of Health, along with unrestricted contributions from the Bill & Melinda Gates Foundation, the Burroughs Wellcome Fund, GlaxoSmithKline, and the World Health Organization.

In addition to funding from NIEHS, the project received support from a long list of partners worldwide who contributed additional funding at various levels. The supplement is also available in print and CD-ROM versions by contacting Cherice Holloway at hollowac@mail.nih.gov or (301) 496-0815.

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(Graphic courtesy of Clarice Holloway and the Fogarty International Center)

Senior Trainee to Establish Free Radical Lab

By Eddy Ball

NIEHS research fellow Dario Ramirez, Ph.D., leaves NIEHS in February to begin a new phase in his career and set up his own lab for his new job in Oklahoma City, after working for seven years in the NIEHS Laboratory of Pharmacology and Chemistry (LPC).

On March 1, Ramirez assumes his new position as an assistant member of the Free Radical Biology and Aging Department at the Oklahoma Medical Research Foundation (OMRF). He will begin work with the help of a three-year, \$500,000 Rising Research Star award from the [Presbyterian Health Foundation](#) to fund start-up and postdoc recruitment — as well as a curriculum vitae listing the 18 peer-reviewed articles he has published and the nine awards he received during his tenure at NIEHS.

A native of Argentina, Ramirez attended the National University of San Luis, where he received his first master's in biochemistry and microbiology, a doctorate in biochemistry and immunotoxicology, and a second master's in immunology. It was during his years at the university that Ramirez first became interested in [OMRF](#). “My [graduate school] advisor had actually worked there as a postdoc,” he explained.



Ramirez, shown at Science Day in 2007, took advantage of the many resources at NIEHS. “The good thing about the mentoring by Ron [Mason],” he said, “was that I had the freedom to pursue my career interests, and he was very supportive of all my initiatives.” (Photo courtesy of Steve McCaw)

Networking and Mentors' Support

For Ramirez, the road to ORMF began early in his tenure at NIEHS with a combination of mentoring, networking, hard work and serendipity.

Ramirez' awards — and the encouragement of his mentors, Mason, Laboratory of Structural Biology Head Ken Tomer, Ph.D., Leesa Detering, Ph.D., LPC Head John Pritchard, Ph.D., colleagues on the [Genetics and Environmental Mutagenesis Society](#) board of directors, and Deputy Scientific Director Bill Schrader, Ph.D. — helped him engage in a number of professional development activities.

Ramirez, who describes himself as “a good listener,” developed an intricate network of colleagues and potential collaborators virtually everywhere he went. “I presented my research at as many different meetings as I could,” he explained. “I wanted my research to be noticed and I expected my scientific contributions to be applied to solve important aspects of oxidative stress and inflammation in human diseases, where free radicals are important players.”

It was his Award for Best Postdoctoral Talk at the 2006 GEMS Fall Meeting that ultimately led to his position at OMRF. Ramirez used an LPC advance against the cash award to finance a trip to the American Association of Immunologists 2007 Annual Meeting in Miami Beach. There he met a recruiter from OMRF who took his CV and began the process that landed his new position and the start-up grant for his lab.

In 2001, Ramirez accepted a visiting fellowship at NIEHS under the direction of award-winning Research Chemist and head of the Free Radical Metabolism Group [Ron Mason, Ph.D.](#) Under Mason's direction, Ramirez honed his skills in the basic chemistry of free radicals and expanded the applications of a novel technique for detecting biomolecule-centered radicals, particularly with regard to DNA radicals, that he named immuno-spin trapping — while also keeping several other lines of research going simultaneously to demonstrate the power of this technique for understanding basic issues of redox biochemistry in chemistry, biochemistry and molecular medicine.

Ramirez considers that the production of biomolecule-centered free radicals during the organic response to redox changes and inflammation induced by metabolic and environmental stressors is key to characterizing the molecular mechanisms of a host of conditions, including obesity, asthma, cancer, diabetes and aging. “If we can understand how redox biochemistry is related to inflammation,” he reasons, “then we can understand more completely how these diseases progress, find new diagnostic tools and establish new therapies.”

Along with his most recent honor from the Presbyterian Health Foundation, Ramirez was recognized in 2007 for his Outstanding Scientific Accomplishment in Support of the Mission of the NIEHS and was presented in 2004 with the Young Investigator Award by the Society for Free Radical Biology and Medicine. He received the Fellow Award for Research Excellence twice, in 2004 and 2006, and a Poster Presentation Award during Science Day 2007. In 2006, he was a member of the first group of trainees to receive K-99/R00 Pathway to Independence transition awards.

Asked about his thoughts for the future, Ramirez said, “I am very committed to the public health of the United States, ... [and] I think I can do better science here that will actually help other countries. I am very proud to be part of OMRF, leading an initiative to find a way to address important health issues, such as chronic inflammatory diseases,” he continued, “and following the many other OMRF researchers who have made seminal discoveries in the field of redox biochemistry and spin trapping.”

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Ramirez gave an award-winning lecture at the Fall 2006 GEMS meeting, one of many opportunities he used to make himself a highly visible young investigator at NIEHS and beyond. (Photo courtesy of Steve McCaw)

DISCOVER Grants Awarded

By Robin Mackar

The National Institute of Environmental Health Sciences (NIEHS) announced awards totaling \$6.8 million for the first year of funding to three new research centers called **DISCOVER** centers - Disease Investigation Through Specialized Clinically-Oriented Ventures in Environmental Research. The new DISCOVER centers are expected to bridge the gap between basic research and clinical treatment of diseases caused by environmental factors.

“The DISCOVER centers will help to define the role of environmental agents in the initiation and progression of human disease and develop new ways to both prevent and treat disease,” said Dennis Lang, Ph.D., interim director of the NIEHS Division of Extramural Research and Training, as he announced the new awards. “The potential impact of the research that these three centers will be conducting is enormous.”

NIEHS launched the DISCOVER program in January 2006 when the initial grant opportunities were announced. The centers reflect an integrated research approach expected to advance our understanding of how the environment interacts with biological processes to either preserve health or cause disease by bringing together laboratory research and population based studies.

“The research being supported through this program is unique in that each DISCOVER center will support projects that will be patient- or clinically oriented, while also looking at the mechanisms of how certain environmental factors influence disease etiology, pathogenesis, susceptibility, progression, and prognosis,” said David Balshaw, Ph.D., one of the scientists at NIEHS who helped develop the program.

Balshaw points out that the new centers reflect the commitment of NIEHS to children’s health research. “Two of the DISCOVER centers are direct extensions of previously funded Centers for Children’s Environmental Health. The DISCOVER centers will focus their efforts on understanding the clinical impact of environmental exposures in children and extending that research to improve diagnosis and clinical intervention. We believe this work will also inform public policy and community education aimed at reducing the burden of children’s asthma,” Balshaw said.

The three new centers are:

- **Johns Hopkins Bloomberg School of Public Health, Baltimore;** [Patrick N. Breyse, Ph. D.](#) Breyse and his collaborators will form a new DISCOVER Center called the Center for Childhood



Frederica Perera (Photo courtesy of Eric Evans and Columbia University)



Joel Kaufman (Photo courtesy of the University of Washington Seattle)

Asthma in the Urban Environment. This group will examine how indoor and outdoor exposures to particulate matter and allergens may impact the airways of asthmatic children. African-American children living in inner cities often are disproportionately impacted by asthma because of excessive indoor and outdoor pollutants. The researchers will be working closely with the family members and others in the community as they conduct this research.

- **Columbia University Mailman School of Public Health, New York; Frederica Perera, Dr. P.H.** Perera and her collaborators will focus their [research efforts](#) on determining when and how common air pollutants from traffic and other combustion sources including diesel exhaust can affect the lungs of children. The Columbia Center for Children’s Environmental Health DISCOVER grant proposes to develop community partnerships and outreach to regulatory policy for improved disease prevention, as well as develop biomarkers of exposure and disease progression and improved therapies for children’s asthma based on understanding environmental exposures.
- **University of Washington, Seattle; Joel Kaufman, M.D.** Kaufman and colleagues will focus their research efforts on understanding the impact of traffic-related air pollution on cardiovascular disease. Specifically, the program will seek to increase understanding of biological pathways related to inflammation and vascular dysfunction from air pollutants and progression of cardiovascular disease. The ultimate translation of this program will potentially advance therapy and cardiovascular disease prevention through educational outreach opportunities to both the medical and public health communities.



Patrick Breyse (Photo courtesy of Johns Hopkins University)

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Enhancing Oceans and Human Health Initiative

By Eddy Ball

Four years after launching the [Centers for Oceans and Human Health \(COHH\)](#) collaboration with the National Science Foundation, NIEHS continues to expand its strategic partnerships within the larger global oceans community. To further that effort, NIEHS Acting Deputy Director Bill Suk, Ph.D., attended the ninth annual Partnership for Observation of the Global Oceans (POGO) meeting held at the Bermuda Institute of Ocean Sciences (BIOS) in St. Georges, Bermuda January 9 – 11.

As Suk explained afterwards, his objective at the meeting was three-fold: to re-establish ties with the global oceans community with the development of new initiatives in mind; to enhance existing COHH programs through communication with scientists involved in deep-ocean observational research; and to share our analytical expertise with the global oceans community and raise its appreciation of the ocean’s enormous public health impact. Attending the [POGO](#) meeting were more than 35 directors of major oceans observational centers, including the Scripps Institute of Oceanography and the Woods Hole Oceanographic Institute in the United States, the Shirshov Institute of Oceanology in Russia and many others.

According to POGO, programs observing the oceans help researchers better understand the impacts that oceans have in terms of natural disasters, human health and well-being, energy sources, water resources, climate change, marine ecosystems and marine biodiversity. A [Global Earth Observation system](#) is being developed that will include satellites to investigate distant and inaccessible parts of the oceans, robotic probes to explore ocean depths, ingenious monitoring devices attached to marine mammals, fixed stations taking continuous measurements, and unmanned vehicles to record life in the most remote parts of the deep ocean and research vessels.

Echoing a recurring theme in the NIEHS Global Environmental Health Initiative, as well as issues surrounding global climatic change and human health, Suk pointed to the importance of collaboration and coordination in maximizing the impact of limited public funding in the area of oceans and human health. “The global oceans community is an established network of research worldwide,” he observed. Maintaining close ties with that community can further the goals that COHH is pursuing, he continued. “In the future, we may accomplish as much by encouraging new directions in collaboration with the global oceans research community.”

Increasing lines of communication with the global oceans community could lead to expansion of areas of research at the COHH sites, Suk observed. Current COHH programs focus primarily on coastal and continental shelf issues, particularly harmful algal blooms, or “red tide.” Deep-ocean observational researchers are increasing their understanding of the role of deep-ocean temperature fluctuations in climate change and beginning to see a much clearer connection with human health and well-being globally — even far within a continent hundreds of miles from an ocean.

“We can all benefit if we can approach ocean issues as partners, rather than as individual programs working independently — uninformed about each other’s work and running the risk of duplicating efforts or failing to see important connections.” Underscoring the value of a systems approach in global environmental health, Suk observed that efforts to understand the network of causes, effects and influences in global environmental health should be accompanied by efforts to expand networks of partners and supporters.



During a reception at POGO, Suk, center, posed with Anthony Knap, Ph.D., left, president and director of BIOS; and Anthony Haymet, Ph.D., director of the Scripps Institute of Oceanography. As Suk noted, “These partnerships are also a way of broadening our constituency.” (Photo courtesy of POGO)



Bermuda resident — and American film star — Michael Douglas, right, was honored at the meeting for his support of ocean research. After receiving his award, Douglas shared his passion for the oceans with José Achache, Ph.D., director of the Group on Earth Observations (GEO), Geneva, Switzerland. (Photo courtesy of POGO)

Although the NIEHS entered the ocean arena in an interdisciplinary research mode in 1978 with the establishment of the Marine and Freshwater Biomedical Sciences (MFBS) Center program, the initiative gained added momentum as the result of a 1998 Presidential National Ocean Conference. The following year, an international conference on “Oceans and Human Health” at BIOS in Bermuda featured Suk as organizer and session chair. Suk co-authored a paper in 2002, [“Indicators of Ocean Health and Human Health: A Research Framework,”](#) that outlined the current program design.

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Julianne Malveaux Speaks at King Celebration

By Robin Arnette

On Wednesday January 16, NIEHS employees celebrated the life and legacy of Dr. Martin Luther King, Jr., at a standing-room-only event held at the neighboring Environmental Protection Agency (EPA) Main Auditorium. Attendees were treated to a program that reminded everyone of the movement for change that King passionately believed in and how much more needs to be done 40 years after his death.

Each year NIEHS and EPA employees gather together to hear a distinguished speaker deliver the keynote address for the King celebration. This year they continued the tradition with nationally known economist, author and commentator [Julianne Malveaux, Ph.D.](#) Malveaux, a native of San Francisco, California, has written several books on race, gender and economic issues, and her name is widely recognized from her weekly syndicated column that ran until 2004 in newspapers across the country.

In addition to her writing, Malveaux has appeared on many national radio and television programs, serves on several boards, including the Economic Policy Institute, and is the founder and thought leader of Last Word Productions, Inc., a multimedia production company headquartered in Washington, D.C. According to Malveaux, her most important job, however, is centered on education. She is the 15th president of [Bennett College](#) for Women in Greensboro, North Carolina.

Malveaux opened her remarks with a story that King mentioned in his January 1965 interview with *Playboy Magazine*. The theme of the anecdote was a major focus of King’s work—dignity and equality for all, especially in the workplace. Malveaux said, “King was sitting on a plane that had been delayed due to mechanical difficulties. While he was waiting, he looked out of the window and saw a group of people scrambling around the plane, attempting to fix it. The flight attendants served drinks and peanuts to the passengers while the pilot gave regular updates over the intercom. After awhile the pilot said, ‘We’ve fixed the plane and we’re going to leave in a few minutes.’ Everyone applauded, but King said to himself, ‘What about the ground crew?’”



*MLK Celebration Speaker Julianne Malveaux
(Photo courtesy of Wanda Mobley and
Bennett College)*

Malveaux pointed out that the crowd was applauding the pilot, but they failed to realize that the pilot hadn't fixed the plane. The ground crew had. "Indeed it was the 'ground crew' that so frequently propelled Dr. King to do the work that he did," she said.

Malveaux then centered the audience's attention on King's historic words spoken in his "I Have a Dream" speech during the August 28, 1963 march on Washington. Many people focus on his imagery of true brotherhood, but she reminded the group of what led him and the marchers to the steps of the Lincoln Memorial. She stated, "In that very same speech, Dr. King said, 'We have come to the nation's capital to cash a check and that check has been marked insufficient funds.' If every time someone said I have a dream and someone else responded, cash the check, imagine how different our discourse and ideas would be." Malveaux echoed King by declaring, "You cannot have racial equality unless you have economic justice."

King had hoped this poor people's campaign would bring people of all ethnicities together to place demands on government agencies that would bring about change in health and human services, employment and the environment. Malveaux pointed out it was also King's tireless efforts for the poor that brought him to Memphis, Tennessee that fateful day in April 1968. "King reluctantly entered the garbage workers' strike, but he went because he thought he could make a difference," Malveaux said. "King didn't die dreaming; he died trying to raise wages and improve working conditions."

Malveaux ended her talk by challenging the audience to contribute to King's legacy of restructuring society through service. "When Monday comes and you take a day on and not a day off, think about the 'ground crew.' The service you give won't change lives unless you're willing to talk about what you do the rest of the year."

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Our Friends across the Lake: The EPA-RTP MLK Celebration Organizing Committee

Several employees representing various offices within the EPA were responsible for organizing this year's MLK event and several of them spoke or participated in the event:

- Lillian Bradley, Office of Air Quality Planning and Standards (OAQPS)
- Rosalina Rodriguez, OAQPS
- Steve Page, OAQPS
- Brodwynn Roberts, National Health and Environmental Effects Research Laboratory (NHEERL)
- Hal Zenick, Ph.D., NHEERL
- Wanda Pemberton, Office of Administration & Resources Management (OARM)

Durham Careers in Science Consortium Meets at NIEHS

By Eddy Ball

Finding ways to augment science curriculum and activities — and consequently turn young people on to careers in science — is the goal of a diverse group of educators, business people, scientists and community leaders who gathered at NIEHS January 14 for a meeting of Durham Careers in Science (DCIS). The meeting was hosted by Marian Johnson-Thompson, Ph.D., NIEHS director of Education and Biomedical Research Development.

Chaired by Kathy Hoffmeier, vice president of Workforce Development for the [Durham Chamber of Commerce](#), the group explored the establishment of a broad-based speakers' bureau to help support science educators in the [Durham Public School \(DPS\) System](#).

As Hoffmeier explained at the beginning of the meeting, DCIS is an industry-driven program dedicated to supporting science education in grades K-12. The program's goal is to enhance both General Science and Career and Technical Education Science standard courses of study through the active involvement of local businesses. Hoffmeier said she envisions modeling the DCIS resource on the [Environmental Protection Agency's EPA-RTP Speaker's Bureau](#), but with an emphasis on the private sector.

“The bottom line is business connecting with the kids and getting involved,” Hoffmeier told the group. “I think in the long run what you do with a committee like this is going to make a big impact.”

Two DPS administrators, Director of Science Janet Scott and Director of Career Technical Education Bob Gant, gave the group an overview of the middle-school and high-school science curriculum. As Scott described the benefits for students, visiting speakers, hands-on activities and field trips can help young people better understand the connections between science and real-world careers for themselves. Speakers often can bring to the classroom an expertise that the teacher may not have.

Gant reinforced the schools' need for real-life science experiences and pointed to the need for young people to develop more realistic career expectations than the common aspiration to succeed as a professional athlete, which was the number one career choice in a recent survey of eighth graders. “We want to say ‘Go ahead, have that dream. But, just in case, what are some other things you're interested in doing?’” he said.



As people began to fill the Executive Conference Room in the Rall Building, Johnson-Thompson, left, queued up the PowerPoint programs with the help of Packenham, who is program director in the NIEHS Office of Scientific Director. (Photo courtesy of Steve McCaw)



Hoffmeier organized the meeting and handled publicity and registration. Following talks by DPS educators, she facilitated a question-and-answer session — and pressed attendees to make specific commitments to the program. (Photo courtesy of Steve McCaw)

As the meeting turned to brain-storming about how to go about creating the speakers' bureau, several of the six NIEHS scientists and administrators in the audience had suggestions. Sharon Beard and Joan Pakenham, Ph.D., expressed concerns about the time-consuming vetting process for school volunteers who have direct contact with students. Liam O'Fallon, chair of the Environmental Health Science Education Committee, suggested that high school science courses introduce students to the gene-environment interaction model of human disease. Most of the other group members who commented agreed that the system for linking speakers and teachers should be as direct as possible.

In addition to the Durham Chamber and DPS, representatives of the City of Durham, Durham Technical Community College, North Carolina Central University (NCCU), Duke University and several Durham non-profit organizations that offer educational programs, such as [Futures for Kids](#) and the [Shodor Education Foundation](#), attended the planning meeting. The federal sector was also represented by scientists from the U.S. Army Research Office and Environmental Protection Agency. Private workplace representatives attended from Biogen Idec, GlaxoSmithKline and EMC Corporation.



A veteran science educator who began her career as a biology teacher, Scott delivered the keynote talk on content needs in the science programs of the Durham Public Schools. (Photo courtesy of Steve McCaw)



Gant gave several examples of the creative approaches that speakers in such career development courses as Exploring Biotechnology have used to engage students' attention. (Photo courtesy of Steve McCaw)



Shown left to right, Ashley Sue Allen, community liaison for NBC 17, EPA Environmental Engineer Kelly Leovic and Johnson-Thompson listened as Hoffmeier outlined how she envisioned the speakers' bureau working. (Photo courtesy of Steve McCaw)



Li-An Yeh, left, of the BRITE program at NCCU and Michelle Keech of Biogen Idec listened as RTI Senior Health Researcher Phillip Graham, Dr.P.H., asked about the mechanics of recruiting speakers. (Photo courtesy of Steve McCaw)

Science Notebook

Inflammasome and Infection

By Robin Arnette

In Rodbell Auditorium on January 8, 2008, NIEHS welcomed Richard A. Flavell, Ph.D., as part of the continuing 2007–2008 NIEHS Distinguished Lecture series. Flavell discussed the intricacies of innate and adaptive immunity in a lecture titled “The Inflammasome in Pathogen Recognition and Inflammation.” Principal Investigator Donald Cook, Ph.D., of the Laboratory of Respiratory Biology hosted the event.

Flavell, a Sterling Professor and Chairman of the Department of Immunology and Professor of Molecular, Cellular and Developmental Biology at Yale School of Medicine in New Haven, Conn., has garnered many prestigious awards. Also, being a Fellow of the prestigious [The Royal Society](#), the United Kingdom’s National Academy of Science, allows him to use the post-nominal letters “FRS” and share membership with British citizens who have made significant contributions to mathematics, engineering and medicine. One of the most famous Fellows is world-renowned physicist Stephen Hawking, Ph.D.

Flavell laid the groundwork of his talk by saying, “We are very much outnumbered by microorganisms in this world, and several of those microorganisms have worked out ways of living in and on us.” However, the immunological implications of this concept depend on the exact location of the bacterium or eukaryotic parasite. For example, *Mycobacterium tuberculosis*, the organism that causes tuberculosis, lives inside a cellular vesicle called a macrophage. The immune system has to use different ways of dealing with those organisms than it would with microorganisms that live outside of cells. Some agents, such as *listeria* bacteria and viruses, live in a cell’s cytoplasm rather than within a vesicle.

Mammals have three classes of molecules that detect infections, with the transmembrane Toll-like receptor class being the most well-known. The class of cytoplasmic NOD-like receptors (NLRs) is the most numerous, however. Flavell focused on three of its members: NALP3, IPAF and ASC. In addition to having leucine-



Flavell described the results of a network approach to immune function, an approach that studies the inter-relationships of the proteins that make up the inflammasome. (Photo courtesy of Steve McCaw)



Cook described his guest as “one of the true leaders in immunology” working in “one of the finest departments of immunobiology anywhere in the world.” (Photo courtesy of Steve McCaw)

rich repeats, they have nucleotide binding domains which are generally believed to be involved in pathogen recognition. “This pathogen recognition leads to an activating multi-enzyme complex called an inflammasome,” he said. “We wanted to study the proteins that make up an inflammasome to find out what they did.”

Previous studies suggested that Toll-like receptors recognized a foreign invader and transferred the signal to the cytoplasmic NLRs. The NLRs formed the inflammasome and activated caspase-1 which led to the secretion of cytokines, including interleukin-1 (IL-1), i.e., IL-1 β and IL-18, and cell death. Flavell and colleagues studied NALP3 knockout mice and determined that these mutants lacked caspase-1 activity and failed to secrete IL-1. IPAF knockout mice were also defective in caspase-1 activity. These data confirmed that NALP3 and IPAF were integral players in the formation of the inflammasome.

Inflammasomes are also important in triggering adaptive immunity and may be demonstrated using a system called contact hypersensitivity in which chemicals are painted on the skin of a mouse. This action leads to a T-cell mediated immune response that can be re-challenged several days later by painting a different area of the mouse, traditionally the ear. Using a caliper a researcher can measure the thickness of the ear which indicates inflammation. The reaction is specific to the stimulus or hapten. According to Flavell the nonsensitized mouse doesn't get a thick ear, but treating a normal wild-type mouse produces a thickening of the ear. “When this is done on the ASC knockout or the NALP3 knockout, the thickening is greatly reduced,” he said. “So this intracellular recognition mechanism through the production of IL-1 plays a role in triggering adaptive immunity.”

Flavell's lab will continue to apply molecular approaches to understand the immune response. Despite his group's progress, Flavell concluded, “The challenge is establishing the mechanisms by which this all works.”

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Evolution of Human Genome's 'Guardian' Network

By Mike Resnick and the Cincinnati Children's Hospital Medical Center

Human evolution has created enhancements in key genes connected to the p53 regulatory network -- the so-called guardian of the genome -- that boost the network's safeguards against DNA damage that could cause cancer or a variety of genetic diseases, according to an international team of scientists led by the National Institute of Environmental Health Sciences (NIEHS) that included Cincinnati Children's Hospital Medical Center. Their study, titled “[Functional Evolution of the p53 Regulatory Network through Its Target Response Elements](#),” appeared in the Jan. 22 *Proceedings of the National Academy of Sciences (PNAS)*. Because genetically engineered mouse models are increasingly powerful tools in understanding the risks and mechanisms of human diseases, and rodents do not have the same evolution-based safeguards in p53 function as humans, the study also underscores the need for additional considerations in the interpretation of research using rodent models.

“Our findings are especially important because rodents are often used as model organisms to investigate the genetic origins of diseases that affect humans, as in research by cancer investigators evaluating the impact of DNA-damaging agents,” said Anil Jegga, D.V.M,



Research Geneticist and lead author Michael Resnick (Photo courtesy of Steve McCaw)

a researcher in the Division of Biomedical Informatics at Cincinnati Children's and key contributor to the study. "Rodent models remain important to our understanding of disease processes, although our study suggests the need to address experimentally the differences in p53 regulatory pathways between humans and rodent models."

"The findings reveal a new piece of the p53 puzzle and help us to understand how genes became part of the network," suggested Michael A. Resnick, Ph.D., who led the study and is head of the Chromosome Biology Group at NIEHS. Resnick and his team have been characterizing the functions of p53, a well-known suppressor of tumors, and have created systems in mouse, human and yeast cells that address contributions of normal and tumor mutant p53 in regulation of genes. The functional models, concepts and rules developed in Resnick's lab, previously described in PNAS in terms of a hand playing a piano, provided a conceptual base for launching the study.

The comparative functional genomics aspect of the study was driven by Jegga and his colleagues who looked systematically at small DNA sequences associated with the promoters, or enhancers, of specific genes that carry out orders from p53. These promoter elements act like antennae -- responding to activated p53 by boosting target gene expression and function inside a cell's nucleus. Using the functional rules and comparing the response element sequences across nearly 50 different binding sites of genes in the p53 network within 14 species (from zebra fish to humans), the researchers were able to reveal critical evolutionary changes in the function of genes involved in the repair of DNA damage.

The 14 species represented an estimated 500 million years of evolutionary separation, helping investigators determine how the function of p53 response elements was conserved or changed as different species developed. Jegga said researchers were surprised to find the acquisition of functional response for certain genes involved in DNA metabolism or repair to be mostly unique in humans. While the p53 functional responsiveness of many genes is shared with chimpanzees and rhesus monkeys, researchers said the p53 control of DNA metabolism and repair functions is lacking in rodents.

In humans, when DNA damage is detected, the p53 network seems to have gained additional capabilities that allow it to slow cell growth, initiate repairs or, if needed, apoptotic cell death. Apoptotic, or programmed cell death capability in the p53 network, is thought to be evolutionarily conserved throughout the development of vertebrate species and was probably established after the divergence of vertebrates and non-vertebrates. DNA metabolism and repair capabilities controlled by p53 may have emerged more recently in evolutionary history to create primate-specific response characteristics, the researchers explained.

"The fact that DNA metabolism and repair genes have undergone this kind of evolution in humans may reflect an increased need for coordinated control of molecular repair activities during DNA replication to allow for the maintenance of genomic integrity during complex differentiation, growth and aging," said Bruce Aronow, Ph.D., co-director of Computational Medicine at Cincinnati Children's and a study co-author.

A clue to p53 functional differences may be found in sunlight. Exposure to the ultra-violet rays in sunlight activates the DNA-damage responses of the repair gene *Ddb2* in humans, but the same gene does not function in rodents. Some studies have suggested that rodents may have a reduced need for genetic protection from sunlight because they are nocturnal and have a fur shield.



*Research Fellow Daniel Menendez
(Photo courtesy of Steve McCaw)*

“Although the full implications of these evolutionary points remain far from clear, our work demonstrates that there has been both refinement and evolution of gene networks controlled by p53,” Aronow said. “Exciting work is underway by research groups within the National Cancer Institute’s Mouse Models of Human Cancer Consortium to develop mice that are genetically engineered to test the combined effects of altering p53 and telomerase, the enzyme that controls the length and stability of repeating DNA sequences in the telomere region. Mouse models will continue to become progressively more powerful tools for studying human cancer and additional information about the p53 network will help us refine our interpretation of pre-clinical research that may lead to improved cancer prevention for at-risk and normal individuals.” The present results demonstrate the need for caution in interpreting the observations with mice.

The functional studies in mammalian cells were provided by Daniel Menendez, Ph.D., a research fellow at NIEHS. Alberto Inga, Ph.D., a former NIEHS research fellow, now with his own lab at the National Institute for Cancer Research (Molecular Mutagenesis Unit, Department of Translational Oncology) in Genoa, Italy, provided the initial functional work in yeast that formed the basis for much of the study.

Funding support came in part from the National Cancer Institute’s Mouse Models of Human Cancers Consortium, the Italian Association for Cancer Research, the National Institute of Environmental Health Sciences, and the Computational Medicine Center, a State of Ohio Third Frontier Wright Center for Innovation.

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Superfund Study of Toxins in China’s Freshwater Ecosystem

By Melissa Fabiano

Scientists from Dartmouth College, Lakeland College, and the Chinese Academy of Sciences in Beijing investigated the bioaccumulation and trophic transfer of the toxic metals, mercury and arsenic, in Lake Baiyangdian, China. The study, “Mercury and Arsenic Bioaccumulation and Eutrophication in Baiyangdian Lake, China,” published on-line in December 2007 in the journal *Water, Air, Soil Pollution*, targeted the largest lake in the North China Plains. The lake receives runoff from the industrial city of Baoding, which produces significant amounts of man-made pollutants that can affect the water and food supply of the region and enter the food chain.

In [their field study](#), the team of investigators, which included Dartmouth biologists and NIEHS Superfund grantees Celia Chen, Ph.D., and Carol Folt, Ph.D., tested three separate sites, all of which were in the proximity of Baoding’s industrial outlets on Baiyangdian Lake. Each of these sites was associated in varying degrees with three pollution sources: coal emission, sewage release, and agricultural runoff. The researchers determined that the toxins of most concern at these sites due to their effect on the freshwater ecosystem were mercury in fish and arsenic in water.



Former NIEHS Research Fellow Alberto Inga, Ph.D. (Photo courtesy of Steve McCaw)

“The mercury and arsenic in this system are high enough to be of concern to humans and wildlife that drink the water and consume the fish. For example, we saw arsenic levels in the water that represented more than 50 times the EPA-recommended limit for consumption in fish and shellfish,” explained Chen, the study’s lead author.

Because of the health risks posed by arsenic and mercury present in levels above EPA-established critical threshold in fish caught for human consumption, the researchers examined the quality of life of resident organisms in the lake with regard to these toxins and the effects of nutrient enrichment of lakes, a process known as eutrophication.

According to the study, eutrophication, which results from nitrogen and phosphorus in sewage and agricultural run-off entering a body of water and can eventually deplete the water’s oxygen supply, promotes the proliferation of algal blooms that potentially mitigate concentrations of dissolved metals in the water due to uptake by the algae. However, the extent of mitigation varies due to the chemical characteristics of the toxin and ecological factors related to an organism’s trophic level, or relative position in the food chain.

The team sampled and analyzed a group of 13 fish for mercury and found that all had levels of mercury above the critical threshold level and posed some risk to humans and wildlife. A second group of 39 fish were sampled and analyzed for arsenic content. These samples showed an arsenic content high enough to pose significant health risk.

The investigators also noted that total mercury bioaccumulation did not consistently increase with trophic levels at Baiyangdian Lake. Yet, they did find an increase in mercury concentration related to fish size, which they linked to the total bioaccumulation of mercury over a fish’s lifetime and age-related shifts in diet, as older fish eat prey with a higher mercury concentration. Arsenic concentrations in the plant and animal life decreased with increasing trophic levels reflecting a trend of biodiminution in the food chain, which the researchers speculated may result from a higher level of arsenic excretion relative to assimilation.

According to the study, these results add further evidence that there are lower dissolved and particulate concentrations of mercury and arsenic when there is a presence of increasing algal blooms. The findings also shed light on how these toxins move through the food web in a freshwater ecosystem known to be polluted. The study concluded that “Our results suggest that both Hg and As contamination should be investigated further due to the potential health risks to humans from drinking lake water or consuming the fish.”

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Folt, right, and Chen are affiliated with the Dartmouth Center for Environmental Health Science and the Superfund Basic Research Program’s Toxic Metals Research Program. (Photo courtesy of Joseph Mehling and Dartmouth College)

Portier Outlines Strategy for HTS Pathway Analysis

By Eddy Ball

The January 9 talk by NIEHS Associate Director Chris Portier, Ph.D., in Rodbell Auditorium was the first in a series of seminars sponsored by the National Toxicology Program (NTP) Biomolecular Screening Branch. The presentation, “Identifying Toxicity Pathways - Linking Genes, Pathways and Disease,” was also the first presentation by NTP of a strategy for systematically analyzing pathways and identifying targets for high-throughput screening (HTS) in toxicology testing, which is an important component of the NTP Roadmap.

Portier, director of the Office of Risk Assessment Research, reported on the results of an exhaustive literature review and multiple database mining effort that took his team over a year to complete. The effort, spearheaded by two postdoctoral fellows working with Portier, Julia Gohlke, Ph.D., and Reuben Thomas, Ph.D., examined the relationships among thousands of genes and several hundred disease phenotypes to produce their “top twenty” list of disease pathways. The data was pulled largely from the 177 Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways.

According to Portier, the project’s scientists are helping to advance HTS toxicology testing in several ways. The team’s research succeeded in defining pathways for disease and identifying clusters of related genes, metabolic processes, phenotypes and environmental factors specific to humans. The scientists also identified high-potential signature pathways for the NTP and other HTS investigators, and they explored chemical linkages from the pathways back to diseases.

Moreover, Portier emphasized, the team developed a repertoire of rules and schemes for determining targets in the pathways through both analytical and experimental approaches to pinpoint which of all the activities that are going on at the cellular level should weigh more heavily in pathway linkage analysis ([see text box](#)). Their systematic approach promises to help investigators confirm hypotheses as well as generate new ones.

Selecting the Best Working Targets: Strategies for Developing a Hierarchy of Importance

Portier offered several different rules and schemes to apply in order to determine the relative importance of targets that show a significant change in relation to disease endpoints:

- Heavy Ends Rule, which gives targets at the edges, the beginning or end of a pathway greater weight than targets in the middle
- Sequential Best Rule, which ranks targets that are adjacent in a pathway more weight than targets with more distant associations
- Crossroads Analysis, which values targets more highly if they appear at the point where two pathways cross each other
- Loner Analysis, which gives more weight to targets that appear only in one pathway associated with a disease
- Watershed Analysis, which manipulates targets by computer or by knock-out to see which targets have the “most flow” downstream in the pathway
- Emerging-disease pathway analysis to link targets in shared pathways with environmental factors
- Constructing phenotype-phenotype, phenotype-environmental factor and environmental factor-environmental factor interaction networks to confirm hypotheses and generate mode-of-action hypotheses linking environmental factors with targets

To illustrate the domino-like disease pathway concept, Portier used the example of the *BRCA1* gene, a polymorphism of which has been strongly associated with breast cancer risk. “It’s not the *BRCA1* [polymorphism] itself that’s affecting the cancer risk,” he explained. “It’s how *BRCA1* changes the biochemistry of the cell.”

“We’re looking for things [genes, proteins and other metabolites] where multiple targets in existing pathways are related to the same or a similar disease, and then we choose that pathway as a major target for HTS,” he continued. Portier then presented a series of rules for determining which of all the activities that are going on at the cellular level should weigh more heavily in an analysis of the pathways. As Portier explained, investigators need guidelines for selecting the targets that are more clearly related to the disease in question and not ones that are shared with other disease pathways.

Asked about how he plans to validate the predictive ability of HTS findings, Portier proposed comparing the results on chemicals with full animal testing data with HTS pathways analysis of the same chemicals. “If we could show that the chemical, through whatever type of -omics analysis we did, linked to the pathways and then linked to the diseases seen in the animals,” he explained, “we’d be in a good position to argue that indeed there is at least some degree of validation going on.”

HTS toxicology testing promises to help the NTP and others reduce the use of animals in testing and begin to address the backlog of over 60,000 registered chemicals that have not been thoroughly tested for their possible toxicological, mutagenic or carcinogenic effects. But before investigators can realize the potential of HTS with human cell lines, they need to build on the kind of systematic approach Portier outlined for finding the needles in the haystack of millions of target analytes that -omics platforms are capable of identifying.

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Portier pondered his response to a member of the audience who asked him about how investigators plan to validate the findings of HTS pathways analysis. (Photo courtesy of Steve McCaw)



Throughout his presentation, Portier credited postdoctoral fellows Julia Gohlke and Reuben Thomas for the research supporting his findings: “This research is truly Julia’s and Reuben’s research.” (Photo courtesy of Steve McCaw)

Upcoming Distinguished Lecture Features Mitchell Lazar

By Eddy Ball

The 2007-2008 NIEHS Distinguished Lecture Series continues at 11:00 a.m. February 13 with a talk by Mitchell Lazar, M.D., Ph.D., on “Nuclear Receptor Regulation of Metabolism.” Lazar’s talk will take place in Rodbell Auditorium and be hosted by Trevor Archer, Ph.D., chief of the NIEHS Laboratory of Molecular Carcinogenesis.

Lazar is the Sylvan H. Eisman Professor of Medicine and Genetics, chief of the Division of Endocrinology, Diabetes and Metabolism, and the director of Institute for Diabetes, Obesity and Metabolism at the University of Pennsylvania School of Medicine. He is the 2006 recipient of The Endocrine Society’s Edwin B. Astwood Award.

For the past 20 years Lazar’s scientific research has focused on gene and metabolic regulation and mechanisms of hormone action. His laboratory is particularly interested in receptors for small, lipophilic hormones such as thyroid hormone and retinoic acid.

Lazar also discovered the hormone resistin, which plays an integral role in insulin resistance, and his lab continues to study the molecular physiology of resistin in a number of model systems. Resistin is made only in fat cells, is secreted into the bloodstream, and reduces insulin sensitivity — making it a potential link between peroxisome proliferator activated receptor (PPAR), obesity and diabetes.



*Distinguished Lecturer Mitchell Lazar
(Photo courtesy of Vesselina Panteva and the University of Pennsylvania)*

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Extramural Update

Workshops on Global Variability in Response to Air Pollution

On September 4, 2007, NIEHS extramural and intramural staff met with twelve international air pollution research experts in Mexico City to discuss the breadth and depth of different air pollution studies around the world, and to assess the feasibility of comparing and pooling data to better understand the diverse clinical responses and genetic susceptibility to exposure to air pollution across different populations.

Building on the discussion at that meeting, NIEHS has scheduled a follow-up workshop June 16-17, 2008, titled “Genetic Susceptibility to Air Pollution Outcomes: Approaches to Translation of Cardiopulmonary Animal Disease Models.” The workshop will be held at NIEHS in Research Triangle Park, N.C.

The goals of the upcoming workshop are to foster collaborations between human disease and mouse model researchers and identify appropriate strategies and approaches for combining research efforts in human population and animal studies to further advance the understanding of the underlying biological pathways.

The 2007 meeting was held in conjunction with the International Society of Environmental Epidemiology (ISEE). Gwen Collman, Ph.D., chief of the NIEHS Susceptibility and Population Health Branch in the Division of Extramural Research and Training (DERT), chaired the meeting.

Workshop participants included Kimberly Gray, Ph.D., Kimberly McAllister, Ph.D., Daniel Shaughnessy, Ph.D., and Jerry Phelps of DERT and Stephanie London, M.D., and Steve Kleeberger, Ph.D., of the Division of Intramural Research. The invited attendees were Kathleen Belanger, Ph.D., Yale University; David Christiani, M.D., and Douglas Dockery, Sc.D., Harvard University; Frank Gilliland, Ph.D., University of Southern California; Nelson Gouveia, Ph.D., University of Sao Paulo; Joel Kaufman, M.D., University of Washington; Nino Kuenzli, M.D., Ph.D., Center for Research in Environmental Epidemiology; Sumi Mehta, Ph.D., Health Effects Institute; Annette Peters, M.D., GSF-Institute for Epidemiology; Isabelle Romieu, M.D., Sc.D., National Institute of Public Health, Mexico; and Chit-Ming Wong, Ph.D., University of Hong Kong.



*Air pollution also affects visibility in Mexico City.
(Photo courtesy of Jerry Phelps)*

The working group included experts in the field of the health effects of air pollution. Collman asked the group to assist NIEHS staff in gauging the status of the science and the impact of genetics on responses to air pollution.

Discussion topics included:

- Differences in susceptibility and response endpoints of interest.
- The possibility of comparing and combining data from international studies.
- How current studies are framing questions to explain the role of genetic factors in response to AP.
- Consortia Models – How can researchers work together to maximize resources?
- Standardization – Are measures of air pollution standardized? Do global standardized clinical phenotypes exist?
- Outcomes — Is it desirable and feasible to add genetic analyses to existing exposure studies and vice versa, and, if so, what is the best approach?

Attendees offered a series of recommendations to the NIEHS staff including mechanisms to improve statistical methodologies and training opportunities. There was group consensus that bringing the “mouse community” and epidemiologists together in a meeting would be beneficial in stimulating translation of basic studies to epidemiology especially for gene discovery and translation. Panelists agreed that successful labs and groups have regular interactions with other groups across disciplines. To allow good animal models to have potential to be translated into human studies, the panelists agreed that a meeting between mouse geneticists and epidemiologists, as well as other researchers using key model organisms such as *C. elegans* would be useful.

There was general discussion and consensus that replication of results is very important and could benefit from a consortium of population studies. There was also discussion of challenge studies and developing methods such that challenge studies can be incorporated into larger epidemiology studies.

In closing the meeting, Collman observed that NIEHS might want to have additional meetings of experts to develop specific action plans, one of several items that are sure to be on the agenda at the June meeting. That meeting will address a specific need identified at the ISEE workshop to bring together human geneticists and epidemiologists with investigators focusing on a variety of animal disease models to understand air pollution-induced respiratory and cardiovascular outcomes.

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NIEHS Papers of the Year 2007

By Jerry Phelps and Robin Arnette

NIEHS investigators and grantees published nearly 2,800 peer-reviewed scientific studies in 2007. Fifteen studies are highlighted here with findings that range from new insights into basic mechanisms to the demonstration of potentially useful applications of research in the clinical setting:

IL-6 and Gender Differences in Liver Cancer Rates

A study by NIEHS grantees may shed light on why the most common form of liver cancer, hepatocellular carcinoma, strikes men with three to five times the frequency as women.

The research team treated mice with the potent liver carcinogen diethyl nitrosamine, which produced liver tumors in all the males, but in only 10-20 percent of the female mice. The researchers discovered that the male mice produced much more of the inflammatory protein interleukin-6 (IL6) than the females. When IL6 was eliminated in the male mice by treating with estrogen, the liver cancer rate dropped by about 90 percent bringing it in line with the rate in the female mice.

Citation: Naugler WE, Sakurai T, Kim S, Maeda S, Kim K, Elsharkawy AM, Karin M. 2007. Gender disparity in liver cancer due to sex differences in MyD88-dependent IL-6 production. *Science* 317(5834):121-124.
[\[Abstract\]](#) [\[Synopsis\]](#)

Supported by grants P42ES010337, R37ES004151 and R01ES006376. Michael Karin, Ph.D., University of California San Diego.

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Polymerase Stalling and Transcriptional Regulation

Gene expression begins with the assembly of a multi-protein complex at the gene promoter followed by RNA synthesis. Recruitment of RNA polymerase II to a promoter is necessary for the activation of many genes, but sometimes polymerase activity is inhibited by regulated stalling of polymerase elongation. Using a genome-wide search for genes with RNA polymerase II stalled within the promoter-proximal region, NIEHS scientists demonstrated that stalling is widespread, and occurs at hundreds of genes that respond to stimuli and developmental signals. Thus, polymerase stalling is an important mechanism for transcriptional regulation and may play a role in the control of transcriptional responses to dynamic environmental and developmental cues.

Citation: Muse GW, Gilchrist DA, Nechaev S, Shah R, Parker JS, Grissom SF, Zeitlinger J, Adelman K. 2007. RNA polymerase is poised for activation across the genome. *Nat Genet* 39(12):1507-1511. [[Abstract](#)]

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S-nitrosothiols: Possibilities in Fighting Asthma and Heart Disease

NIEHS-funded research suggests the endogenous compound S-nitrosothiol may have clinical implications for a variety of diseases including asthma and heart failure. Researchers found that S-nitrosothiol, a specialized form of nitric oxide, inhibits a key regulatory system that ordinarily decreases the number of beta adrenergic receptors on the surface of cells once they have been stimulated.

Administration of S-nitrosothiols to mice prevented the receptors from being turned off. If these findings are confirmed in humans, they may lead to the development of new non-sensitizing therapeutic agents for many conditions such as heart disease, asthma, high blood pressure, chronic pain, diabetes and others.

Citation: Whalen EJ, Foster MW, Matsumoto A, Ozawa K, Violin JD, Que LG, Nelson CD, Benhar M, Keys JR, Rockman HA, Koch WJ, Daaka Y, Lefkowitz RJ, Stamler JS. 2007. Regulation of beta-adrenergic receptor signaling by S-nitrosylation of G-protein-coupled receptor kinase 2. *Cell* 129(3):511-522. [[Abstract](#)] [[Synopsis](#)]

Supported by grant U19ES012496. Jonathan S. Stamler, M.D., Howard Hughes Medical Institute and Duke University Medical Center.

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Breast Enlargement in Prepubertal Boys

The authors investigated possible causes of gynecomastia—development of prominent breast tissue in the male—in three healthy prepubertal boys with normal serum concentrations of endogenous steroids. The boys' gynecomastia coincided with the topical application of products that contained lavender and tea tree oils, but was resolved shortly after discontinuing the use of products containing these oils. Furthermore, studies in human cell lines indicated that the two oils had estrogenic and anti-androgenic activities. Repeated topical exposure to lavender and tea tree oils probably caused the condition.

Citation: Henley DV, Lipson N, Korach KS, Bloch CA. 2007. Prepubertal gynecomastia linker to lavender and tea tree oils. *N Engl J Med* 356(5):479-485. [[Abstract](#)] [[Synopsis](#)] [[News Release](#)]

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Mutant Astrocytes Play a Role in the Degeneration of Motor Neurons in Amyotrophic Lateral Sclerosis (ALS)

Mutations in the gene for superoxide dismutase (SOD1) are known to cause ALS, also known as Lou Gehrig's disease, in which progressive degeneration of motor neurons leads to paralysis and certain death. In an NIEHS-funded study, researchers expressed this mutant protein in a variety of single cell types in culture. Motor neurons degenerated and died when they were co-cultured with astrocytes expressing mutant SOD1, while mutant SOD1 in neurons, fibroblasts or microglia did not cause neuronal death.

The findings suggest that stem cell therapy focused on replacing damaged neurons may not be feasible in ALS because mutant astrocytes would most likely kill the replacement neurons.

Citation: Nagai M, Re DB, Nagata T, Chalazonitis A, Jessell TM, Wichterle H, Przedborski S. 2007. Astrocytes expressing ALS-linked mutated SOD1 release factors selectively toxic to motor neurons. *Nat Neurosci* 10(5):615-622. [[Abstract](#)] [[Synopsis](#)]

Supported by grant R21ES013177. Serge Przedborski, Ph.D., Columbia University.

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Unique Substrate Specificity of DNA Polymerase Mu

NIEHS scientists, in collaboration with investigators at the University of North Carolina, published this study describing the crystal structure of DNA polymerase mu, an important player in the repair of double-strand breaks (DSB). The results revealed the structural basis of the substrate specificity of this polymerase, which is unique among all DNA polymerases studied to date. The data provided new insights into the repair of potentially cytotoxic DSBs that can be induced by chemotherapeutic agents and by physical and chemical agents in the environment.

Citation: Moon AF, Garcia-Diaz M, Bebenek K, Davis BJ, Zhong X, Ramsden DA, Kunkel TA, Pedersen LC. 2007. Structural insight into the substrate specificity of DNA polymerase mu. *Nat Struct Mol Biol* 14(1):45-53. [[Abstract](#)] [[Synopsis](#)]

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Predictive Gene Also Maintains Differentiation of Mammary Ductal Cells

A gene known as *GATA-3* is in a family of genes responsible for driving the processes that take stem cells down the path of differentiation that lead to mature cells regardless of their ultimate fate. NIEHS-supported researchers have now determined that *GATA-3* is also required for the maintenance of differentiation in ductal cells of the mammary gland. Using laboratory mice genetically altered so that they lack *GATA-3*, the research team found that mature cells reverted to the less specialized undifferentiated state, which is a characteristic of aggressive cancer cells. The new finding suggests that the gene may play a key role in the development of breast cancer and possibly other malignancies.

Citation: Kouros-Mehr H, Slorach EM, Sternlicht MD, Werb Z. 2006. GATA-3 maintains the differentiation of the luminal cell fate in the mammary gland. *Cell* 127(5):1041-1055. [[Abstract](#)] [[Synopsis](#)]

Supported by grant U01ES012801. Zena Werb, Ph.D., University of California, San Francisco.

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Genes in Blood Can Predict Harmful Levels of Acetaminophen

NIEHS scientists found that gene expression patterns derived from blood cells can provide useful indicators of acute acetaminophen exposure in rats. Prediction accuracy ranged from 88.9 to 95.8 percent, outperforming predictions based on traditional clinical parameters. Using blood expression levels of human versions of the rat discriminatory genes, the team was able to separate acetaminophen-intoxicated patients from control individuals with inflammation being the major biological signal in the genes. This study suggests that gene expression changes in peripheral blood cells are sensitive indicators of exposures to liver-damaging levels of acetaminophen and may be useful in the clinic.

Citation: Bushel PR, Heinloth AN, Li J, Huang L, Chou JW, Boorman GA, Malarkey DE, Houle CD, Ward SM, Wilson RE, Fannin RD, Russo MW, Watkins PB, Tennant RW, Paules RS. 2007. Blood gene expression signatures predict exposure levels. *Proc Natl Acad Sci USA* 104(46):18211-18216. [[Abstract](#)] [[Synopsis](#)] [[News Release](#)]

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Inhibition of RelB Synthesis by ER α Signalling Controls the Shift in Breast Cancer Cell Phenotypes

NIEHS-funded research findings connect RelB protein with the estrogen receptor alpha (ER α) — and raise the possibility the protein may be useful as a marker for the detection and treatment of metastatic breast cancer. In invasive ER α -negative breast cancer cells, the team found active synthesis of RelB; however, ER α signaling led to an inhibition of RelB synthesis, leading to an inverse correlation between RelB and ER α gene expression in human breast cancer tissues and cell lines.

This work provides further understanding of the role of RelB in human breast cancer and indicates that inhibition of RelB synthesis represents a mechanism by which ER α can control the shift of epithelial cells to a more invasive phenotype.

Citation: Wang X, Belguise K, Kersual N, Kirsch KH, Mineva ND, Galtier F, Chabos D, Sonenshein GE. 2007. Oestrogen signalling inhibits invasive phenotype by repressing RelB and its target BCL2. *Nat Cell Biol* 9(4):470-478. [[Abstract](#)] [[Synopsis](#)].

Supported by grant P01ES011624. Gail E. Sonenshein, Ph.D., Boston University School of Medicine.

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RNA Direct Transfer of Genetic Information

In an important twist on DNA targeted double-strand break (DSB) repair, NIEHS researchers established that RNA could play a direct role in the repair of a DSB by serving as a template at the break site. The study greatly expanded previous research findings that had demonstrated mediation of recombination by RNA, but only indirectly through a complementary DNA intermediate. Because RNA can be amplified at any time within cells, the findings could lead to new directions in gene targeting.

Citation: Storici F, Bebenek K, Kunkel TA, Gordenin DA, Resnick MA. 2007. RNA-templated DNA repair. *Nature* 447(7142):338-341. [[Abstract](#)] [[Synopsis](#)].

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Supplementation Counteracts Bisphenol A-Induced Epigenetics Changes

Recent NIEHS-funded research shows that epigenetic patterning induced by bisphenol A during early stem cell development leads to problems with fertility and breast and prostate cancer in rat pups whose mothers were fed the compound in their diets. A new study reports that maternal dietary supplementation with either of the methyl donors folic acid or genestein reversed the epigenetic effects in the offspring by stopping the hypomethylating effect of bisphenol A.

The authors conclude that the results support the inclusion of epigenetic effects of chemicals into risk assessments and support further investigation into possible dietary supplements that might counteract the adverse effects of environmental agents on the epigenome.

Citation: Dolinoy DC, Huang D, Jirtle RL. 2007. Maternal nutrient supplementation counteracts bisphenol A-induced DNA hypomethylation in early development. *Proc Natl Acad Sci U S A* 104(32):13056-13061. [[Abstract](#)] [[Synopsis](#)]

Supported by grants R01ES015165, R21ES013053, and T32ES007031. Dana C. Dolinoy, Ph.D. and Randy L. Jirtle, Ph.D., University Program in Genetics and Genomics, Duke University.

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DNA Polymerase Epsilon and Leading Strand DNA Replication

The identity of the “leading strand” polymerase in higher organisms remained uncertain for several decades until investigators at Umeå University in Sweden and NIEHS published a study indicating that among many possibilities, it is specifically DNA polymerase epsilon that participates in replicating the leading strand of the nuclear genome in budding yeast. DNA polymerase epsilon is conserved among higher organisms, including humans. This fundamental discovery of how the genome is replicated places us one step closer to understanding the origins of genome instability that underlie diseases in humans whose occurrence is influenced by the environment.

Citation: Pursell ZF, Isoz I, Lundström EB, Johansson E, Kunkel TA. 2007. Yeast DNA polymerase epsilon participates in leading-strand DNA replication. *Science* 317(5834):127-130. [[Abstract](#)] [[Synopsis](#)] [[News Release](#)].

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Study Links Gene Expression Changes in Babies to Arsenic Exposure

MIT researchers and scientists with Thailand’s Chulabhorn Research Institute report that the children of mothers whose water supplies were contaminated with arsenic during their pregnancies harbored gene expression changes that may lead to cancer and other diseases later in life — even if the children never experience any direct exposure to the pollutant. In addition to establishing the potential harmful effects of these prenatal exposures, the new study also provides a possible method for screening populations to detect signs of arsenic contamination.

This is the first time evidence of such genome-wide changes resulting from prenatal exposure has ever been documented from any environmental contaminant.

Citation: Fry RC, Navasumrit P, Valiathan C, Svensson JP, Hogan BJ, Luo M, Bhattacharya S, Kandjanapa K, Soontararuks S, Nookabkaew S, Mahidol C, Ruchirawat M, Samson LD. 2007. Activation of Inflammation/ NF-kappaB Signaling in Infants Born to Arsenic-Exposed Mothers. *PLoS Genet* 3(11) [[Abstract](#)] [[Story](#)]

Supported by grants R01ES011399 and P30ES002109. Leona Samson, Ph.D. and Rebecca Fry, Ph.D. Massachusetts Institute of Technology

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Identification of a New Base Excision Repair Cofactor

Base excision repair, an important DNA repair pathway for maintenance of the genome, corrects DNA strand breaks and single base DNA damage. This study found that the high-mobility group box 1 (HMGB1) protein specifically interacts and accumulates at sites of oxidative DNA damage in living cells. The results suggest that the chromosomal architectural protein HMGB1 is a base excision repair cofactor capable of modulating base excision repair capacity.

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

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Parkinson-like Degenerative Changes Linked to Reduced Dopamine Storage

Genetically altered VMAT2 LO mice with a decreased ability to package and store dopamine undergo a degenerative process that mimics Parkinson's disease, report NIEHS-supported neuroscientists. The mice were carefully bred to be deficient only in the VMAT2 gene, which is responsible for packaging dopamine for future release by neurons.

Previous research found that this mouse strain included a chromosomal deletion spanning the a-synuclein gene locus. The mice were screened to verify the presence of a-synuclein; this study represents the first data on VMAT2 LO mice with normal a-synuclein expression, a quality that could make them useful for testing compounds to slow the course of the Parkinson symptoms.

Citation: Caudle WM, Richardson JR, Wang MZ, Taylor TN, Guillot TS, McCormack AL, Colebrooke RE, Di Monte DA, Emson PC, Miller GW. 2007. Reduced vesicular storage of dopamine causes progressive nigrostriatal neurodegeneration. *J Neurosci* 27(30):8138-8148. [[Abstract](#)] [[Synopsis](#)]

Supported by grants T32ES12870, F32ES013457, R21ES013828, U54ES012068, R01ES010806 and U54ES012077. W. Michael Caudle, Jason R. Richardson, Ph.D., Gary W. Miller, Ph.D., Emory University, and Donato DiMonte, M.D., The Parkinson's Institute

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Inside the Institute

An Outside Look at 530 Davis Drive

By Eddy Ball

For the 350 or so NIEHS employees and contractors who work in the satellite office spaces at East Campus and Nottingham Hall, the final months of 2008 will mean making a move into consolidated office space at 530 Davis Drive in Keystone.

The new space is the second building south of the Davis Drive intersection with Hobson Road and across the road from the Keystone offices occupied by the National Toxicology Program Archives and Image Associates, the Institute's arts, photography and graphics contractor. The building can be accessed at its Davis Drive entrance or at a Hopson Road entrance that also serves the building occupied by the law firm Kennedy Covington — and is less than the equivalent of two city blocks from the Institute's Hopson Road entrance.

The new location will mean a faster commute for residents of some parts of Cary, Morrisville and Chatham County, but could add a few minutes to the trek for residents of Durham and Chapel Hill and points east and south in Wake County. Most employees will want to steer clear of the Hopson Road/Miami Boulevard intersection by using the Davis Drive exits at I-40 or I-540.

The building's proximity to the main campus should make the journey a little easier for employees who travel there on a regular basis. As newcomers become more familiar with Davis Drive as it runs through "downtown" Morrisville, they're sure to discover new lunchtime options, such as the grocery store deli and eateries just down the road in a new shopping center at the intersection with McKimmon Parkway.

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The building still bears the former occupant's name.
(Photo courtesy of Steve McCaw)



The building's Davis Drive entrance is clearly marked.
The Hopson Road entrance marker is similar to the one on Davis. (Photo courtesy of Steve McCaw)



The building's formal entrance is typical of RTP "parkitecture." (Photo courtesy of Steve McCaw)



With their woody surrounding, the outside areas are sure to be a popular place for those who bring their lunches or take a fresh air coffee break. (Photo courtesy of Steve McCaw)

Black History Month Events

By Eddy Ball

Campus and area organizers have finalized arrangements for three events during February to celebrate Black History Month — a yearly acknowledgement of the struggles and accomplishments of African Americans:

February 1, 6:00 – 8:00, in the Lyda Moore Merrick Gallery at Hayti Heritage Center in Durham: Opening reception for an Exhibition of Works by the African American Quilt Circle. Sponsored by the St. Joseph’s Historic Foundation, Inc., the exhibition runs through April 6.

February 12, 10:00 – 11:30, in the Environmental Protection Agency (EPA) Main Auditorium: Lecture on “Carter G. Woodson and the Origins of Multiculturalism” by Charles Nelms, Ph.D., chancellor of North Carolina Central University.

February 26, 10:00 – 11:30, in the EPA Main Auditorium: Panel discussion on African-American Senior Executive Service facilitated by William Brown, president and founder of the African American Federal Executive Association.

The NIEHS Diversity Council and the Research Triangle Park Chapter of Blacks In Government hosted a talk, “The Seamstress and the Scholar Who Changed America,” on January 30 in Rodbell Auditorium in observance Martin Luther King, Jr. The guest speaker, Professor James Seymour, holds a Doctor of Ministry degree and serves as head of the Department of Religion and Philosophy at Saint Augustine’s College in Raleigh, N.C. He is also the executive director of Accumulated Resources of Kindred Spirits (ARKS), a nonprofit organization that provides resources to humanitarian, educational, and religious projects in America, Africa and India.

Organizers are also planning several events in recognition of Black History Month. Details will follow by e-mail notification as they are finalized.

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Women work on a quilt for the exhibition. (Photo courtesy of St. Joseph’s Historical Foundation, Inc.)

Family Health Transitions Seminar Series Begins February 6

By Eddy Ball

The NIEHS Office of Management and the Disability Advocacy Committee are sponsoring a series of six seminars on family health transitions topics. The presentations will take place on Wednesdays during February and March in the Executive Conference Room and will feature local experts with non-profits and businesses.

- **Feb 6: 1:00 - 3:00** – “Eldercare Issues” –by Gavin Densmore of [Helping Hands of America](#)
- **Feb 13: 2:00 - 3:00** – “The Many Faces of Loss, Grief and Bereavement: Finding Your Way Back to ‘Normal’” – by Edna Ballard, [Joseph and Kathleen Bryan Alzheimer’s Disease Research Center](#).
Duke Medical Center
- **Feb 20: 1:00 - 2:00** – “Loneliness from Loss,” by Barbara Keyworth, NIEHS Employee Assistance Program
- **Feb 27: 1:30 - 3:00** – “Physical Accommodations for Family Health Transitions” – by Laurie Ringaert, [Universal Design Consulting](#)
- **Mar 12: 1:30 - 3:00** – “Coping with Childhood Grief” - Family Health Transitions, Duke Health
- **Mar 26: 10:00 - 11:00** – Legal and Family Financial Questions - Family Health Transitions, Erica Wehner, J.D.; Armor Trust Attorneys in Raleigh, NC

For more information contact Dona McNeill, Cynthia Radford, Ginny Ivanoff, Cindy Innes, Jeannie Bell-Nichols or Alicia Moore.

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White Tigers Land Again in Rodbell

By Eddy Ball

Rodbell Auditorium was the scene once more of youngsters flying through the air, boards cracking into pieces from well-placed kicks and grunts punctuated by the thud of landing feet as students from the White Tiger Taekwondo School in Cary took over the stage January 18 during their third visit to the Institute.

One of the new students this year, six-year-old Fred Chang, is the son of NIEHS Research Fellow Hye-Youn Cho, Ph.D., of the Laboratory of Respiratory Biology. Fred and his fiend, Felix Braun, also six, have qualified for the red-and-black Bodon Belt and continue to hone their skills as they strive to qualify in May for the first-degree Black Belt. Cho’s older son, Justin Chang, who qualified last year for his second-degree belt, was also on-hand for the demonstration.



These students demonstrate the choreography of Martial Arts as they move dance-like in unison. (Photo courtesy of Steve McCaw)

According to the school's newsletter, the Black Belts are recognized by the World Taekwondo Federation and the International Olympic Committee (or Korean Hapkido Federation). The school awards the belts in a solemn ceremony that involves the lighting of the Black Belt candles and the taking of the Black Belt Oath.

The White Tigers subscribe to the holistic philosophy that "martial arts are not only about competition or even self-defense, [but] ultimately... about self-improvement. Properly taught, Martial Arts improve the body, mind and spirit."

As noisy as the White Tigers were, for Fitness Room Manager Stephanie Bullock-Allen, who hosts these visits by the students, the sounds of children and young people doing something that involves vigorous movement is sheer music and a joy to behold.

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For a master or an advanced student, kicking boards can become almost a routine. (Photo courtesy of Steve McCaw)



The group poses at the end of the performance, showcasing Justin Chang, center front, and brother Fred for their proud mother, who was part of the audience. (Photo courtesy of Steve McCaw)



But the offensive move can also turn into an acrobatic performance. (Photo courtesy of Steve McCaw)



He may be a novice, but Fred Chang already has several of the Martial Arts moves down pat. (Photo courtesy of Steve McCaw)



And the same can be said of Felix Braun. (Photo courtesy of Steve McCaw)



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