Environmental Factor
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NIEHS Spotlight

Birnbaum Reflects on First Year as Director

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2009 ONES Awardees Speak at NIEHS

This year's six winners of the Outstanding New Environmental Scientists (ONES) awards gathered at NIEHS Jan. 21 to deliver presentations on their research projects.

HHS Calls for More Research on BPA

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Lewis Explores Federal Partnerships in Health Research

In a January 15 lecture at NIEHS, Denise Riedel Lewis, Ph.D., discussed her diverse experience as an epidemiologist and health scientist in a number of government organizations.

Science Notebook

The Environment and T-cell Differentiation

Distinguished Lecturer Dan Littman, M.D., Ph.D., explained the contributions of several factors involved in the maturation of T cells in a seminar Jan. 19 at NIEHS.

Birnbaum Leads NIH Delegation

NIEHS/NTP Director Linda Birnbaum, Ph.D., led a delegation of NIH scientists to the Joint Workshop on Environmental Pollution and Cancer in China and the U.S. held Jan 5-8 in Guangzhou, China.

Kastner Kicks Off Clinical Seminar Series

"When the immune system turns against its host, it can be a horrific thing," said Daniel Kastner, M.D., Ph.D., during the inaugural talk of the NIEHS Clinical Director's Seminar Series.

Pritchard Announces 2010 Intramural Research Awards

On January 19, NIEHS Acting Scientific Director John Pritchard, Ph.D., announced Intramural Research Awards (IRA) for two new collaborative initiatives by NIEHS principal investigators.

NIEHS Spotlight

Miller Confronts the Lessons of Asbestos in Libby, Mont.

A capacity audience was on hand at NIEHS Jan. 22 as guest lecturer Aubrey Miller, M.D., spoke on "Environmental Health Responses: Asbestos and the Libby Saga."

Local Stakeholders Offer Input on SRP

At the Superfund Research Program (SRP) planning session Jan. 5, NIEHS staff heard from a distinctly local and vocal group of stakeholders — Research Triangle area grantees and a contingent of NIEHS colleagues.

NIEHS Expands Bioethics Program

As part of the NIEHS commitment to building a top notch ethics office, resources and services on bioethics are now available to all NIEHS scientists, staff, fellows, and trainees.

NYC Charity Honors Olden

The New York City charitable organization One Hundred Black Men (OHBM) will honor NIEHS/NTP Director Emeritus Ken Olden, Ph.D., at its 30th annual Benefit Gala on Feb. 25.

Superfund Researcher Named AAAS Fellow

Superfund Research Program grantee Barry Dellinger, Ph.D., was one of eight Louisiana State University researchers recently named as fellows by the American Association for the Advancement of Science.

Science Notebook

Talk Highlights Utility of Copy Number Variant Studies

In a Jan 11 guest lecture at NIEHS, Baylor College of Medicine Professor James Lupski, M.D., Ph.D., explored the clinical impact of copy number variants in the human genome.

Researcher Looks for Key to Longevity

"Aging is one certainty in life that we can all count on, but not one that is particularly well understood by the scientific community," observed Xiaoling Li, Ph.D., in her Jan. 7 talk at NIEHS.

DNA Damage Found in Patients with Friedreich's Ataxia

An NIEHS/NIH-funded team of investigators published a groundbreaking study on gene expression and DNA damage among patients with the rare inherited disease Friedreich's ataxia.

Genetic Variation Influences Response to Environmental Exposure

On January 14, NIEHS grantee David Threadgill, Ph.D., explored "Preclinical Modeling of Environmental Exposures" during the latest installment of the NIEHS Keystone Science Lecture Series.

This Month in EHP

Environmental Health Perspectives (EHP) revisits lead this month in a feature article titled "Exposure on Tap: Drinking Water as an Overlooked Source of Lead."

NIEHS Spotlight

And Off We Go — Conference Season Begins

With each new year, opportunities come to showcase NIEHS research advances and new funding programs for scientists across the country. This year is no exception.

NIEHS Community Remembers Terri Damstra

The environmental health sciences community lost one of its distinguished senior members Dec. 9 with the unexpected death of former NIEHS/WHO scientist Thressa (Terri) Damstra, Ph.D.

Science Notebook

Lippincott-Schwartz to Give 2010 Rodbell Lecture

Jennifer Lippincott-Schwartz, Ph.D., will present the annual Rodbell Lecture on Feb. 9 at NIEHS with a talk on “Advances in Super-Resolution Imaging.”

Kirk Smith to Speak at Duke

Veteran NIEHS grantee Kirk Smith, Ph.D., will be at Duke University on Feb. 17 to present a seminar on global health that is open to the public free of charge.

Inside the Institute

Wright Wraps Career as Information Guru

NIEHS Biomedical Librarian Larry Wright, Ph.D., bid farewell to friends and colleagues on a familiar note at a retirement reception in the NIEHS Library on Dec. 30.

NIEHS Celebrates Legacy of M. L. King Jr.

Oprah-bound motivational speaker Tawana Williams returned to NIEHS on Jan. 7 as part of the Institute’s annual celebration of the achievements of Martin Luther King Jr.

NIEHS to Implement New IT Governance Committee

Although most employees aren’t aware of all that the NIEHS IT Governance Committee does, staffers will soon begin to reap the benefits of its efforts.

Extramural Research

Extramural Papers of the Month

- Secrets of Drought Resistance Revealed
- Crystal Structure of Variant P450 Determined
- Lead Exposure Linked to Depression and Panic Disorders
- Genetic Risk Score for Multiple Sclerosis Developed

Intramural Research

Intramural Papers of the Month

- Mapping RNA Polymerase II Stalling to Study Gene Regulation
- Store-Operated Calcium Entry Suppressed by Phosphorylated STIM1
- DNA Polymerase β and Poly (ADP-ribose) Polymerase Partner in DNA Base Excision Repair
- Genetic Studies Identify DNA Sequences Associated with Lung Function

NIEHS Papers of the Year 2009

Of the more than 2,700 papers published by NIEHS-supported researchers in 2009, 24 publications were chosen as Papers of the Year:

- Genome-Wide Association Study (GWAS) Identifies Multiple Loci Associated with Lung Function
- Genomic-Based Model Used to Predict Chemical Hepatocarcinogenicity
- Variations in Human Gut Microbiome Linked to Obesity
- Sun Exposure May Trigger Certain Autoimmune Diseases in Women
- Hexavalent Chromium in Drinking Water Causes Cancer in Rodents
- Clean Air Extends Life Expectancy
- Mapping RNA Polymerase II Stalling to Study Gene Regulation
- Skin Penetration Risk For Cadmium Selenide Nanomaterials Examined
- Surfactant Decreases Quenching in Brightly Fluorescent Single-Walled Nanotubes
- SIRT1 Identified as a Key Regulator of Hepatic Lipid Metabolism
- Genome-Wide Association Study Identifies Asthma Gene
- Calcium Signaling During Mitosis
- Genome-Wide Association Study Identifies Genes Increasing Heart Attack Risk
- DNA Scrunching During Gap Repair Synthesis
- Alzheimer's Disease Linked to Mitochondrial Damage
- Link Between Serum Cholesterol and Asthma
- Arsenic Compromises Immune Response
- Initiation of Repair of Random DNA Double Strand Breaks Requires RAD50
- Carbon Nanotubes Can Affect the Lung's Lining
- Hippocampal Synaptic Plasticity Can Be Modified by Differential Calcium Handling
- Electronic "Nose" Smells Toxins
- Female Mice Neonatally-Treated with Genistein Exhibit Reproductive Abnormalities
- Gene Variant Linked to Bladder Cancer
- Methoxyacetic Acid Disrupts Endogenous Estrogen Signaling

Calendar of Upcoming Events

- **February 4**, in Rodbell Auditorium, 10:00–11:00 — Keystone Seminar on “Carcinogenesis: Development Gone Awry” with Ana Soto, M.D., and Carlos Sonnenschein, M.D.
- **February 8**, in Rall F-193, 11:00–12:00 — Laboratory of Signal Transduction Seminar Series on “Adipogenesis and Gene Expression,” by Philip Pekala, Ph.D.
- **February 9**, in Rodbell Auditorium, 2:00–3:00 — Distinguished Lecture Series Annual Rodbell Lecture featuring Jennifer Lippincott-Schwartz, Ph.D., speaking on “Advances in Super-Resolution Imaging”
- **February 16 (Offsite Event)** at North Carolina State University (NCSU) Toxicology Building on the NCSU Centennial Campus, 4:00 — Raja Jothi, Ph.D., addressing “Systems Biology and Epigenetics of Gene Regulation
- **February 17 (Offsite Event)** at Perkins Library, Room 217, on the Duke University campus, 4:30–6:00 — Duke Global Health Institute Seminar on “Incomplete Combustion—the Unfinished Global Agenda for Health, Environment and Climate Protection,” featuring Kirk Smith, Ph.D.
- **February 18 (Offsite Event)**, at Sigma Xi, 12:00–1:00 — American Scientist Lecture Series with Jeffrey Sonis, M.D., speaking on mental health impacts in the wider population of human right tribunals in Cambodia focused on the atrocities of the Khmer Rouge. RSVP for pizza
- **February 18–19**, in Rodbell Auditorium, 8:30–5:00 — National Advisory Environmental Health Sciences Council (NAEHSC) meeting
- **February 22**, in Rall F-193, 11:00–12:00 — Seminar on “Neuroinflammatory Processes in Parkinson’s Disease” with Etienne Hirsch, Ph.D.
- **February 26–March 2 (Offsite Event)** in New Orleans — 66th Annual American Academy of Allergy, Asthma and Immunology
- View More Events: NIEHS Public Calendar

NIEHS Spotlight

Birnbaum Reflects on First Year as Director

By Eddy Ball

On Jan. 12, just a week shy of her one-year anniversary at the head of the NIEHS/NTP, Director Linda Birnbaum, Ph.D., made her first annual state-of-the-Institute presentation to employees and contractors. Birnbaum spoke to a near-capacity crowd in Rodbell Auditorium with a live webcast to staff at off-site locations.

With a record increase in budget and other successes to her credit in 2009, Birnbaum was understandably upbeat as she described the fruits of her travel-heavy year and looked forward to the anticipated outcome of initiatives underway. She introduced several new hires and discussed leadership searches underway to put in place a permanent scientific director, director of the Division of Extramural Research and Training, deputy director, education director, new Bethesda liaison staff, and, later in 2010, a clinical director.

"As far as I'm concerned," Birnbaum told staff, "it's been a great year — very, very exciting, very, very demanding. I've worked harder than I ever believed was possible, and I think it's made a difference in terms of our budget, our reputation, and our recognition as we move forward."

"I think the work we've done on the hill has paid off," Birnbaum told employees. The new budget, she noted, includes a record 4.1 percent increase for NIEHS — the largest percentage increase of any NIH IC. (Photo courtesy of Steve McCaw)

On the front lines in Bethesda and Washington

On average during 2009, Birnbaum spent a day and a half to two days every other week in Bethesda and Washington helping to make NIEHS a more integral part of NIH. "Frankly, guys," she observed, "when we're out of sight, we're out of mind" — which she said affects the budget and NIEHS participation in NIH activities.

Birnbaum explained that she testified before congressional committees twice last year and visited more than 25 offices of congressmen and senators, spreading the NIEHS mantra of prevention — that "you can't change your genes, but you can change your environment."

Birnbaum also made progress establishing and expanding partnerships with sister NIH institutes and offices (ICs) and other federal agencies. She pointed to a cost-saving, facilities-sharing agreement with the

A few seats remained unoccupied in Rodbell Auditorium because the talk was webcast throughout NIEHS and to off-site staff members. (Photo courtesy of Steve McCaw)

neighboring U.S. Environmental Protection Agency and added, “I’ve also reached out to our stakeholders and advocacy groups to keep NIEHS at the head of environmental science research and public health advocacy.”

Maintaining visibility worldwide

Birnbaum showed no sign of the jet lag she must have experienced on her trip the previous week to China as part of the NIEHS global health initiative for a joint workshop on cancer and the environment (see Science story) — one of the many times she has crossed time zones traveling the U.S. and the world to spread the NIEHS message of preventing disease, especially complex disease, by better understanding the networks of interactions among genes and individual and collective environments. “I think that some of these presentations that I’m making,” Birnbaum told the audience, “have really helped to re-establish NIEHS as the premier environmental health science research organization in the world.” (watch video of pre-Copenhagen 15 event on “Public Health Impacts of Reducing Greenhouse Gas Emissions” in Washington).

NIEHS Deputy Scientific Director Joel Abramowitz, Ph.D., left, seemed gratified by Birnbaum’s praise for the showcase of research he organized for Science Day in November 2009. Health Scientist Administrator Annette Kirshner, Ph.D., center, shared in kudos for stimulus grant funding, and Birnbaum congratulated Principal Investigator Paul Wade, Ph.D., rear, for achieving tenure in 2009. (Photo courtesy of Steve McCaw)

Combined Federal Campaign (CFC) co-chair Rachel Frawley, second from front, smiled as Birnbaum praised employee generosity that led to record contributions in 2009. (Photo courtesy of Steve McCaw)

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2009 ONES Awardees Speak at NIEHS

By Thaddeus Schug

This year’s six winners of the Outstanding New Environmental Scientists (ONES) awards gathered at NIEHS Jan. 21 to deliver presentations on their research projects to Institute scientists and visitors. NIEHS Director Linda Birnbaum, Ph.D., welcomed the young investigators, describing the ONES award as an “outstanding funding opportunity that will assist the group of exceptional young scientists in launching an innovative research career focusing on environmental health”.

The ONES winners represent a cross-disciplinary group of scientists, with specialized interests in toxicology, genetics, epidemiology, cardiology, neurobiology, and pharmacology. Their work exemplifies what Birnbaum

referred to as a priority issue at NIEHS, which is the need to conduct "complex research on complex diseases and integrate these issues into environmental health."

Established in 2006, the ONES program is a highly competitive award program that funds the most promising new faculty investigators. NIEHS was the first Institute to make such a strong and unique contribution to the identification and support of junior faculty investigators through the ONES program.

In her opening remarks, ONES program director and meeting chair Carol Shreffler, Ph.D., explained that the ONES grants are R01 awards specifically designed to help junior investigators at the start of their careers "put in the foundation for a successful research career." The five-year grant funds research at $250,000 per year and supports equipment purchases and career enhancement activities with an additional $150,000 during each of the first two years. As Shreffler noted, "Young investigators who were successful at getting their first grant often have trouble getting renewals because they lack access to specialized equipment or career enhancement opportunities."

The morning presentations were part of a daylong agenda for the awardees that included lunch with Division of Extramural Research and Training (DERT) staff and afternoon meetings with intramural scientists and postdoctoral fellows. The ONES awardees will make additional presentations at NIEHS over the course of their grants. Videos of their talks will be posted on the Grant Program Events archive online.

(Thaddeus Schug, Ph.D., is a postdoctoral research fellow in the NIEHS Laboratory of Signal Transduction.)

North Carolina State University Assistant Professor Scott McCulloch, Ph.D. was happy to address his former NIEHS colleagues on his research of how DNA polymerase eta (pol η) responds to DNA damage caused by oxidative stress. (Photo courtesy of Steve McCaw)

Birnbaum said she was delighted with the opportunity to spend the entire morning session engaged in scientific discussion with the young investigators. (Photo courtesy of Steve McCaw)

"This award is intended to be highly selective for the most talented scientists," Shreffler told the audience. "We only allow one application per school within an institution." (Photo courtesy of Steve McCaw)

2009 ONES Awardees

University of California, Los Angeles cardiologist Jesus Araujo, M.D., Ph.D., Los Angeles, will focus on the effects of particulate air pollution on high-density lipoproteins and atherosclerosis.

Virginia Commonwealth neurobiologist and former NIEHS Postdoctoral Fellow Michelle Block, Ph.D., will explore the role of protein radicals in microglia in the environmental mechanisms of chronic neurotoxicity.

New York University epidemiologist Yu Chen, Ph.D., intends to continue her investigation into the interactions between arsenic exposure from drinking water and genetic susceptibility related to inflammation and oxidative stress in cardiovascular disease.

University of Kansas Medical Center pharmacologist James Luyendyk, Ph.D., aims to understand the mechanisms of xenobiotic-induced biliary inflammation and fibrosis.

North Carolina State University toxicologist and former NIEHS Postdoctoral Fellow Scott McCulloch, Ph.D., plans to investigate the role of human DNA polymerase eta (pol η) in the mutagenic response to oxidative stress.

University of Michigan geneticist Dana Dolinoy, Ph.D., will be investigating effects on the fetal epigenome of *in utero* exposure to bisphenol A.

ONES awardees, left to right, Yu Chen, Ph.D., James Luyendyk, Ph.D., Michelle Block, Ph.D., and Dana Dolinoy, Ph.D., look on as fellow winner Jesus Araujo, M.D., Ph.D., explains how air pollution leads to atherosclerosis and heart disease. (Photo courtesy of Steve McCaw)

Block, above, has developed several mouse models she plans to use to help identify the role of microglia in neuroinflammation. (Photo courtesy of Steve McCaw)

Pat Mastin, Ph.D., acting deputy director of DERT, attentively watched the morning presentations. (Photo courtesy of Steve McCaw)

NIEHS Principal Investigator Scott Williams, Ph.D., center, and Postdoctoral Fellow and Mercedes Arana, Ph.D., watched as Block outlined her research plan. (Photo courtesy of Steve McCaw)

NIEHS Principal Investigator Tom Kunkel, Ph.D., above was one of two proud ONES mentors on hand for the talks. McCulloch is a former postdoctoral fellow in Kunkel's DNA Replication Group, and Block is a former postdoctoral fellow in the NIEHS Neuropharmacology Group headed by Jau-Shyong Hong, Ph.D. (Photo courtesy of Steve McCaw)

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HHS Calls for More Research on BPA

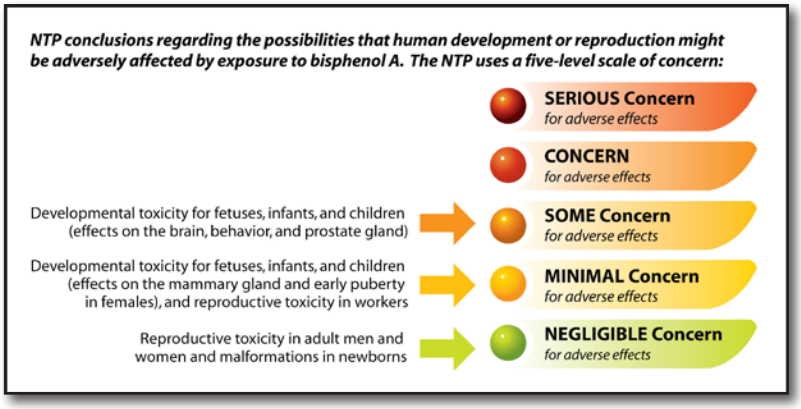
By Robin Mackar

NIEHS/NTP Director Linda Birnbaum Ph.D., joined U.S. Department of Health and Human Services (HHS) officials on Friday, Jan. 15 in a call for more research on bisphenol A (BPA). Birnbaum, HHS Deputy Secretary William Corr, J.D., U.S. Food and Drug Administration (FDA) Commissioner Margaret Hamburg, M.D., and others provided an update on BPA during a series of teleconferences to Congress, the media, partners, and industry. BPA is a chemical that has been used for more than 40 years and is added to many hard plastic food containers such as baby bottles and to the lining of metal and food beverage cans.

"BPA has not been proven to harm either children or adults," explained Corr during a call to the media. "However, given that children in the early stages of development are exposed to BPA, new data in laboratory animals deserves a closer look."

In 2008, the FDA conducted a review of toxicology research and information on BPA and, at that time, judged food-related materials containing BPA on the market to be safe. But recent studies have reported subtle effects of low doses of BPA in laboratory animals. These newer studies are what prompted federal health officials to express some concern about the safety of BPA. The announcement of "some concern" aligns with the conclusions of the NTP Report on BPA.

"We need more research to understand the potential health effects of BPA exposure to children," Corr added. While research on BPA continues, HHS officials offered some reasonable steps that parents can take to minimize their families' exposure to BPA.



Corr also announced that the President has called for the establishment of an Interagency Task Force on Children's Environmental Health. The Task Force will coordinate efforts across the government to focus on environmental health risks that disproportionately affect children, including BPA.

In her remarks, Birnbaum agreed that more research is needed to determine how BPA affects overall human health, in particular young children who are especially vulnerable to the adverse consequences of BPA. Birnbaum highlighted the $30 million research effort on BPA led by NIEHS and NTP.

"It is very important that scientific and regulatory agencies work together, so that all of the available research can and will be considered," Birnbaum said.

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

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Lewis Explores Federal Partnerships in Health Research

By Erin D. Hopper

In a January 15 lecture at NIEHS, Denise Riedel Lewis, Ph.D., discussed her diverse experience as an epidemiologist and health scientist in a number of government organizations. Hosted by NIEHS/NTP Director Linda Birnbaum, Ph.D., Lewis presented a seminar titled "Environmental Health Research: A Panorama of Federal Partnerships." The talk focused on her recent work in the National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) Program and her experiences with other federal agency initiatives.

Lewis is an epidemiologist in the NCI Division of Cancer Control and Population Sciences Surveillance Research Program, which is the home of SEER. Begun in 1973, the SEER program collects and publishes cancer incidence, mortality, and survival data from population-based cancer registries covering approximately 26 percent of the US population.

Lewis focused the talk on her cancer surveillance efforts at NCI but also described her rewarding work at USDA and EPA. (Photo courtesy of Ed Kang)

Surveillance to understand patterns of exposures and cancer

In her description of SEER, Lewis spoke about the spectrum of disease and various types of exposures, some of which are regulated and some of which are not. Exposures under surveillance and regulation include such environmental factors as pathogens, food contaminants, medications, and air pollutants. Unmonitored and unregulated exposures include environmental conditions that are more variable according to each individual's lifestyle, such as diet and exercise.

One benefit of SEER and similar surveillance programs is that the resulting data can be used for hypothesis generation. NCI has developed such tools as the State Cancer Profiles website that scientists can use to map cancer incidence spatially and temporally across the country by geographic location, gender, ethnicity, and cancer type with a number of visualization tools to display the data.

USDA and EPA: Studies of food-borne pathogens and arsenic

In addition to her discussion of the SEER program, Lewis talked about her experience at other government organizations, including the Food Safety and Inspection Service (FSIS) at the U.S. Department of Agriculture (USDA) and the National Health and Environmental Effects Laboratory (NHEERL) at the U.S. Environmental Protection Agency (EPA).

While working at FSIS, Lewis came to view food-borne outbreaks as a type of environmental health investigation. To illustrate the challenges of her role at FSIS, Lewis outlined a hypothetical scenario of an E. coli O157:H7 outbreak in which the outbreak investigation team works collaboratively to determine the source of the pathogen. Once the team identifies the source of the outbreak, the appropriate regulatory agency takes control to determine the proper corrective actions.

Lewis described her work at FSIS as "adrenaline-inducing." She added, "There were times when I felt I needed to have my suitcase packed just in case something came up." When describing the FSIS response to food-borne outbreaks, Lewis emphasized the importance of a well-designed investigation team, which should include epidemiologists, microbiologists, physicians, sanitarians, toxicologists, veterinarians, inspectors, and community-based compliance officers.

The conclusion of Lewis's lecture focused on her years at the EPA, during which she helped to conduct epidemiological and biomarker studies on arsenic in drinking water. During studies in Millard County, Utah, Lewis and her colleagues compared exposure and mortality rates in subjects with arsenic-contaminated drinking water. The results from the Utah Mortality Cohort were particularly valuable because most of the previous arsenic exposure studies had been conducted outside the United States.

(Erin D. Hopper, Ph.D. is a postdoctoral fellow in the NIEHS Laboratory of Structural Biology Mass Spectrometry Group.)

NIEHS Health Scientist Administrator Kim McAllister, Ph.D., appreciated Lewis's suggestions for improving communication and collaboration between NIEHS and other NIH institutes. (Photo courtesy of Ed Kang)

The talk held an obvious appeal for NIEHS Sister Study contractor Pam Schwingl, Ph.D., who is project director with Social and Scientific Systems Inc. (Photo courtesy of Ed Kang)

NIEHS Acting Director Steve Kleeberger, Ph.D., inquired about the transfer of regulatory control between various government agencies during food production. (Photo courtesy of Ed Kang)

Working Toward a More Comprehensive View of Cancer Control

During her tenure at NCI, Lewis helped to organize a Workshop on Developing a Research Agenda to Improve Cancer Control to bring together experts from across the country in an attempt to identify knowledge gaps and technological advances to improve cancer surveillance and control. One of the products of the workshop was a list of the top six ideas for moving its work forward:

- Ensure confidentiality for study participants
- Create tools and theory for time and spatial/temporal aspects
- Develop searchable and user-friendly one-stop portals for data, boundaries, references, and tools
- Devise strategies and tools for communicating uncertainty
- Generate methods for effective use of census data with health data
- Emphasize community-based participatory research

Citation: Pickle LW, Szczur M, Lewis DR, Stinchcomb DG. 2006. The Crossroads of GIS and Health Information: A Workshop on Developing a Research Agenda to Improve Cancer Control. Int J Health Geogr 5:51.

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Miller Confronts the Lessons of Asbestos in Libby, Mont.

By Eddy Ball

A capacity audience was on hand at NIEHS Jan. 22 as guest lecturer Aubrey Miller, M.D., spoke on "Environmental Health Response: Asbestos and the Libby Saga." Hosted by NIEHS/NTP Director Linda Birnbaum, Ph.D., Miller's talk presented a narrative of the ongoing public health emergency response in Libby, Mont., and outlined some of the lessons regulators and scientists should learn from the experience.

An environmental epidemiologist and a captain in the U.S. Public Health Service board-certified in occupational medicine, Miller currently serves as the chief medical officer in the U.S. Food and Drug Administration (FDA) Office of the Commissioner's Office of Counterterrorism and Emerging Threats. Previously, he worked for the U.S. Environmental Protection Agency (EPA) and for the U.S. Department of Health and Human Services (DHHS) as a regional health administrator, coordinating multi-agency emergency responses, such as the Libby situation.

"I've been with several different agencies, and they've certainly colored my world perspective," Miller said of his experiences with the Libby saga, Hurricane Katrina, the anthrax attacks, the attack on the World Trade Center, and other emergencies. (Photo courtesy of Steve McCaw)

The Libby saga continues

The Libby saga began with a newspaper story published in November 1999, and "ten years later, it's still going on," Miller explained. "It's the worst site in EPA history in terms of human health." It has been a source of two of the largest environmental civil and criminal cases, he said, and "it has affected asbestos analysis, methods, and regulations across the country in many ways." The public health emergency in Libby has also given regulators and scientists reason to ponder its lessons for current and emerging environmental threats.

Birnbaum, center, recalled her work with Miller at Libby and said she was "delighted" to host his talk at NIEHS. (Photo courtesy of Steve McCaw)

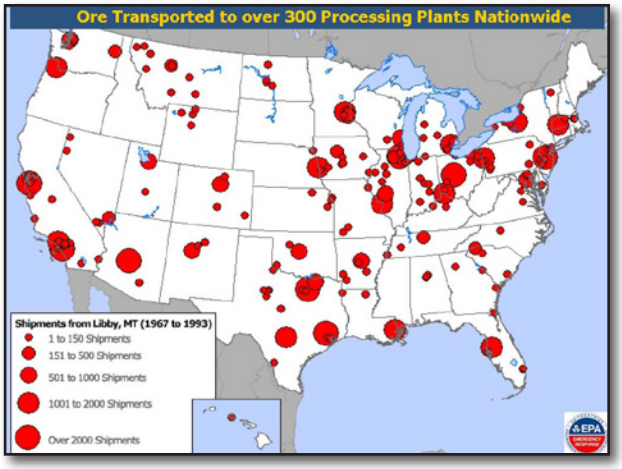
"Even though asbestos has been studied for 100 years," he added, "the science and regulations were developed from worker studies for workplace settings and thus were not very useful for environmental situations and non-worker exposures." Disagreements concerning what minerals should be categorized as asbestos and the determination of "what we should actually be measuring in terms of human exposure" continue to be ongoing public health concerns.

As serious as asbestos exposure has been for workers, even more disturbing to Miller are the risks associated with environmental exposures in the Libby community and elsewhere, as large numbers of non-workers have been identified with asbestos-related disease. Asbestos-contaminated vermiculite was used as attic insulation in over 25 million U.S. homes and contaminated vermiculite was processed in 240 sites across the U.S., where hazardous material was frequently taken and used for landscapes and gardens, driveways, playgrounds, and other purposes.

What appears to the eye as a single fiber, when viewed through an optical microscope, as required by current regulations, turns out with advanced magnification — as seen here — to be a multitude of potentially harmful and highly respirable fibers. (Photo courtesy of Aubrey Miller)

Lessons for environmental health responses in the future

Politics and financial interests further complicate the regulation of such environmental hazards as Libby's. For instance, there was ample evidence accruing for many years that environmental asbestos contamination was hazardous and that the Libby situation was "a predictable surprise." Based on his experiences Miller is convinced that "there must be other Libbys occurring under our noses" in the U.S. Miller stated we need to challenge dogma and preconceptions about environmental exposures and who is at risk in order to identify disease and provide honest and useful solutions for our communities.



Miller used this map showing the distribution of asbestos contaminated vermiculite to processing plants across the United States to underscore his argument that "Libby's not just a Libby problem." (Photo courtesy of Aubrey Miller)

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Local Stakeholders Offer Input on SRP

By Thaddeus Schug

At the Superfund Research Program (SRP) planning session Jan. 5, NIEHS staff heard from a distinctly local and vocal group of stakeholders — Research Triangle area grantees and a contingent of NIEHS colleagues involved in grant administration, basic research in toxicology, and policy analysis. The meeting was the fourth in a series of planning meetings that began in November 2009 (see related story).

These meetings have been organized to gather feedback on a series of questions SRP plans to address as it develops a long-term strategic plan to direct program focus and effectiveness. Jerry Heindel, Ph.D., acting branch chief of the NIEHS Cellular, Organ and Systems Pathology Branch, was quick to initiate discussion, voicing concerns about whether the SRP should include areas of research that are traditional to NIEHS or limit its focus to "programs unique to SRP, such as remediation of waste and improving technology for cleaning up waste sites."

In his opening remarks, NIEHS Acting Deputy Director Steve Kleeberger, Ph.D., reinforced NIEHS leadership support for the "enormous undertaking" involved in the SRP strategic planning initiative. (Photo courtesy of Steve McCaw)

In response, SRP Director William (Bill) Suk, Ph.D., pointed out that to a great extent "SRP operates according to a congressional mandate, and that program balance is dictated by its authorizing legislation." SRP Program Administrator Claudia Thompson, Ph.D., added, "SRP is not attempting to balance specific program topics, but rather a broad range of outcomes so that community groups have what they need to make informed decisions and improve communication through community outreach programs in areas directly impacted by Superfund sites."

SRP plans encourage interdisciplinary science

The audience remained engaged as moderator Larry Reed, from contractor MDB, Inc., shifted discussion to the interdisciplinary approach supported by SRP. Richard Di Giulio, Ph.D., Duke University SRP Center director, noted, "The most significant issues in environmental health research involve areas such as environmental chemistry and biology, biomedical sciences,

NIEHS on the Hill

According to staff attending the Jan. 14 SRP Planning Meeting at the Hubert H. Humphrey Building in Washington, NIEHS Senior Advisor for Public Health John Balbus, M.D., was instrumental in helping to ensure a good turnout of Capitol-area stakeholders, despite an unexpected change in venue.

Among the organizations represented by the 28 participants were the Society of Toxicology, Clean Air Cool Planet, Parkinson's Action Network, Society for Women's Health Research, American Public Health Association, National Association of County and City Health Officials, and Natural Resources Defense Council. Staff were also on hand from the office of U.S. Senator Orin Hatch, U.S. Environmental Protection Agency, and U.S. Department of Labor.

"John reached out to the groups he's worked with over the years in ways the rest of us just couldn't," said NIEHS/NTP Director Linda Birnbaum, Ph.D., who also attended the meeting "It's clear that having leadership representatives in Bethesda is helping us to have a higher profile in Washington and more influence on what happens there in regard to the Institute's environmental health science and public health initiatives."

engineering, and the social sciences. SRP should place priority on these very significant issues, which will force interdisciplinary interactions among scientists," he suggested.

Diversified training opportunities offered to graduate students

U.S. Environmental Protection Agency (EPA) Toxicologist and former SRP trainee, Beth Owens, Ph.D., endorsed SRP's interdisciplinary training concept, observing that she frequently uses the cross-disciplinary communication skills she learned at the University of Kentucky program. "Graduate students are generally trained to be knowledgeable in an increasingly narrow field," Owens said. "SRP can and should provide a mechanism by which students can broaden their knowledge base on environmental and Superfund issues, and work as an interdisciplinary team." Suk added that funding interdisciplinary training programs has been an on-going challenge for SRP, due to traditional barriers in academic institutions.

In response, UNC professor and SRP program director James Swenberg, D.V.M., Ph.D., commented, "Universities are making gains in interdisciplinary training, particularly in the areas of public health, translational biology, and nanotechnology." Di Giulio added, "SRP has done a good job promoting program diversification, as evidenced by research extensions into emerging chemicals and nanotechnology, as well as recalcitrant problems such as complex mixtures and differential human vulnerabilities."

Cross agency communications encouraged

Pitching the need for an Institute-wide effort to enhance interagency interactions, NTP Deputy Program Director for Science Nigel Walker, Ph.D., advised SRP to improve communication to avoid overlap among stakeholders. Walker stated, "At the end of the day, we are all trying to use the public's money to figure out common problems. And, if we can share resources between federal agencies and other institutions, we will be better at solving these issues."

In response to questions about the basic research component of SRP, Director Bill Suk, Ph.D., described the balance between basic and applied research mandated by the program's enabling legislation. (Photo courtesy of Steve McCaw)

SRP Moves Ahead With Strategic Plan

SRP will post feedback gathered from a series of face-to-face meetings, Web seminars, and online questionnaire on its Web site. This information, along with recommendations made by the 2009 SRP External Advisory Panel, will be used to draft a long-term strategic plan, which SRP plans to release later this summer.

2010 SRP Strategic Planning Timeline

- Collect input through January 29
- Consolidate information from meetings, questionnaire, and webinars during February
- Draft mission statement and strategic plan in February and March
- Refine mission statement and strategic plan during March and April
- Present plan to the National Advisory Environmental Health Sciences Council at its May 12–13 meeting and incorporate modifications
- Publish and disseminate strategic plan for comment in June

Director of the Office of Policy, Planning, and Evaluation (OPPE) Sheila Newton, Ph.D., was one of many NIEHS stakeholders who urged SRP to keep the end product of its research in mind. "Research translation without impact is not research translation," she reminded the audience. (Photo courtesy of Steve McCaw)

Owens, center, brought two stakeholder perspectives — as a student and as an EPA toxicologist — to the meeting, while Di Giulio, right, spoke about the balance of research, outreach, and translation in his program at Duke. (Photo courtesy of Steve McCaw)

Reed, right, yielded the floor to SRP staff, including Thompson, left, who responded to questions about program specifics. (Photo courtesy of Steve McCaw)

A thoughtful Tom Hawkins, OPPE program analyst, center, sat with NIEHS Division of Extramural Research and Training (DERT) Program Administrators Mike Humble, Ph.D., left, and David Balshaw, Ph.D., right. DERT administrators questioned the overlap of programs funded by DERT and SRP. (Photo courtesy of Steve McCaw)

(Thaddeus Schug, Ph.D., is a postdoctoral research fellow in the NIEHS Laboratory of Signal Transduction.)

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NIEHS Expands Bioethics Program

As part of the NIEHS commitment to building a top-notch ethics office, resources and services on bioethics are now available to all NIEHS scientists, staff, fellows, and trainees. Bioethics deals with the moral questions and controversies that inevitably arise as scientists explore new advances in biology and medicine.

NIEHS/NTP Director Linda Birnbaum, Ph.D., decided to expand the existing Bioethics Program beyond its original position within the division of intramural research.. The Bioethics Program is now part of the NIEHS Office of Ethics, which serves the entire institute under its recently hired Deputy Ethics Counselor, Bruce Androphy, J.D. (see related story)

In consultation with Androphy, Bioethicist David Resnik, J.D., Ph.D., (see text box) will implement the bioethics component of the NIEHS Ethics Program. Resnik has published seven books and more than 150 articles on ethical, social, legal, and philosophy issues in science, medicine, and technology. Resnik, who came to the NIEHS in 2004, is also chair of the NIEHS Institutional Review Board (IRB), which oversees research involving human subjects.

As a service to employees at NIEHS, Resnik, above, has presented and sponsored regular seminars on timely issues, such as "Disability and Social Justice," "Responsibility for Health: Personal, Social, and Environmental," and "Cutting Edge Consent." (Photo courtesy of Steve McCaw)

The Bioethics Program serves three important functions at NIEHS:

- **Serving scientists, fellows, trainees and staff with confidential consultation and advice on ethical issues that arise in the conduct of research** — Past issues have included protecting human subjects in research, authorship and publication, animal care and treatment, collaborations with other institutions, intellectual property, and reporting research misconduct.

- **Providing education and training pertaining to bioethics** — This includes annual training in responsible conduct of research (required for all NIEHS staff and trainees with substantial involvement in research), and seminars and workshops on ethical issues in environmental health research (see text box).

- **Supporting intramural research on bioethics issues** — Resnik has collaborated on research with NIEHS scientists and colleagues from other institutions. He has also sponsored ten interns and guest researchers.

Highlights of Past Bioethics Training at NIEHS

Topics addressed in the annual training in responsible conduct of research range from data fabrication and falsification, plagiarism, authorship, and data management to collaboration, mentoring, and dual-use research. Past bioethics seminars and workshops addressed such topics as confidentiality, protections for research with human subjects, human embryonic stem cell research, research involving transgenic animals, conflicts of interest in research, social determinants of health, responsibility for health, and social justice and health.

About NIEHS Bioethicist David Resnik

Resnik, who came to the NIEHS in 2004, is also chair of the NIEHS Institutional Review Board (IRB), which oversees research involving human subjects. He has a Ph.D. and M.A. in philosophy from the University of North Carolina at Chapel Hill, and a J.D. from Concord University. Before coming to the NIEHS, Resnik was a professor of medical humanities at East Carolina University School of Medicine (1998-2004) and an associate professor of philosophy at the University of Wyoming.

Contact Bioethicist David Resnik by email or phone: (919) 541-5658. Additional information about the Bioethics Program is available at: http://inside-dir.niehs.nih.gov/ethics/home.htm and http://www.niehs.nih.gov/research/resources/bioethics/index.cfm

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NYC Charity Honors Olden

By Eddy Ball

The New York City charitable organization One Hundred Black Men (OHBM), Inc. will honor NIEHS/NTP Director Emeritus Ken Olden, Ph.D., at its 30th Annual Benefit Gala on Feb. 25. During the black-tie event at the Hilton Hotel in New York, Olden will receive the 2010 Distinguished Physician Community Service Award for his work as founder and dean of the new City University of New York (CUNY) School of Public Health.

Olden, above, is "an exceptional scientist" with a commitment to addressing the health disparities and public health challenges of people in NYC, said Hunter President Jennifer Raab. (Photo courtesy of Harvard University)

Olden served as director of NIEHS/NTP from 1991 to 2005. He remained at NIEHS as a principal investigator in the Laboratory of Molecular Carcinogenesis Metastasis Group until September 2008 (see story). Following a series of meetings that summer, Jennifer Raab, J.D., president of CUNY's Hunter College, recruited Olden to establish the first of its kind school of public health with an urban focus (see CUNY TV Dec. 20, 2009 video Study with the Best).

The right leader to create an "epicenter for modern public health"

As NIEHS/NTP director, Olden increased the Institute's role in the area of health disparities and sharpened its focus on public health policy. Raab listed those qualifications as important reasons she chose Olden to take on the challenge of starting the new school of public health. In his role at Hunter, Olden is building an integrated university program to address what Raab called "a crisis" in public health in NYC, where rates of many chronic diseases, such as diabetes, exceed those in other urban areas.

For the past 15 months, Olden has worked out of offices at Hunter College to mobilize support and establish directions for the initiative. On Nov. 16, 2009, he was among the dignitaries on hand as the new program achieved an important milestone with the groundbreaking for the new $135-million eight-story Lois V. and Samuel J. Silberman School of Social Work, which will house the CUNY School of Public Health.

When Olden accepted the position, he called it "one opportunity I thought I couldn't pass up." He explained that he hopes the school will emerge as "the Mecca, the epicenter for modern public health." The new CUNY School of Public Health will begin offering graduate programs in the new facility in 2011.

OHBM's tradition of honoring community leaders

In addition to Olden, OHBM will recognize the contributions of two other leaders at the Benefit Gala — John Agwunobi, M.D., senior vice president of Walmart and president of Walmart Health & Wellness, with the 2010 Distinguished Service Award; and Mark Wagar, president of Empire Blue Cross Blue Shield, with the 2010 Corporate Citizen Award. Founded in 1963, the OHBM describes its mission as "capitaliz[ing] on the collective power of community to address issues of concern, inequities and to empower African Americans to be agents for change in their own communities."

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Superfund Researcher Named AAAS Fellow

By Eddy Ball

Superfund Research Program (SRP) grantee Barry Dellinger, Ph.D., was one of eight Louisiana State University (LSU) researchers recently named as fellows by the American Association for the Advancement of Science (AAAS) — the world's largest scientific organization. AAAS recognized Dellinger for "seminal contributions to [understanding] the origin of toxic combustion by-products, concentrating most recently on dioxins, combustion-generated nanoparticles, and environmentally persistent free radicals."

When notified of Dellinger's latest honor, SRP Director Bill Suk, Ph.D., congratulated his long-time friend and colleague. "I'm always gratified when the exceptional scientists we fund get well-deserved national recognition," Suk said. "Clearly, Barry is making important contributions to environmental health science that will have the potential to prevent disease and improve public health."

Dellinger, an LSU professor of environmental chemistry, heads the LSU SRP Center focused on Health Impacts of Toxic Combustion By-Products and is the principal investigator on an SRP grant for Development of a Demonstrable Model of Dioxin Formation.

AAAS Fellow Barry Dellinger (Photo courtesy of Barry Dellinger and Louisiana State University)

Dellinger's election as an AAAS Fellow is the latest of many honors he has received for his work. He is the Patrick F. Taylor Chair of Environmental Chemistry at LSU and has been recognized with the American Chemical Society's Astellas USA Foundation Award (see story), the Charles A. and Anne Morrow Lindbergh Foundation Certificate of Merit, the Wohleben-Hochwalt Research Award, and the Environmental Protection Agency STAR (Science to Achieve Results) Award, among others.

According to a university spokesperson, LSU ranked among the top ten institutions in number of honorees, with only seven others having more fellows this year. AAAS is the world's largest general scientific society and publisher of the journal Science. AAAS was founded in 1848, and includes some 262 affiliated societies and academies of science, serving ten million individuals. Science has the largest paid circulation of any peer-reviewed general science journal in the world, with an estimated total readership of one million.

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And Off We Go — Conference Season Begins

By Robin Mackar

With each new year, opportunities come to showcase NIEHS research advances and new funding programs for scientists across the country. This year is no exception.

The NIEHS conference season begins in earnest February 18-22 in San Diego with the American Association for the Advancement of Science (AAAS) Annual Meeting. Suzanne Fenton, Ph.D., of the NIEHS Division of Intramural Research (DIR) will be presenting research on the impact that early life exposures have on the development and function of the mammary gland. John Drake, Ph.D., also of DIR, will present on the phylogeny of mutation rates, and staff from NIEHS Division of Extramural Research and Training (DERT) will present a poster about some of the NIEHS Partnerships for Environmental Public Health Program. Staff from the NIEHS Office of Communication and Public Liaison (OCPL) and Environmental Health Perspectives will be on hand at the Institute's award-winning booth to speak with conference attendees about new NIEHS research findings and new funding opportunities.

In March, when NIEHS and National Toxicology Program (NTP) staff head to The Society of Toxicology Annual Meeting in Salt Lake City, not only will there be new science advances to be shared, but NIEHS will debut some innovative ways to showcase its findings. NIEHS and NTP representatives, including Director Linda Birnbaum, Ph.D., will be providing live updates throughout the SOT conference. The updates will be posted on the NIEHS and NTP Web sites at www.niehs.nih.gov/LiveatSOT and on Twitter@LiveatSOT. They'll be reporting on all the innovations, breakthrough research, awards being given out, and interesting people that make SOT so unique. OCPL will be providing more information about this program in the next few weeks.

"We're excited to be working with our scientists and program staff to provide live updates from SOT," said OCPL Director Christine Flowers. "It allows us an opportunity to begin using some new social media tools." New OCPL staff member Ed Kang is working with Flowers and others in OCPL to develop and disseminate information about the "Live Updates from SOT."

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

More to Come in 2010

Other major conferences this year that will be sure to have an NIEHS presence include:

- American Thoracic Society
  May 14-19, 2010 | New Orleans
- The Endocrine Society
  June 19-22, 2010 | San Diego
- International Society of Exposure Science (ISES) and International Society for Environmental Epidemiology (ISEE) 2010 Joint Conference
  August 28 – September 1, 2010 | Seoul, Korea
- Society for Neuroscience 40th Annual Meeting
  November 13-17, 2010 | San Diego
- American Public Health Association 138th Annual Meeting and Exposition
  November 6-10, 2010 | Denver

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NIEHS Community Remembers Terri Damstra

By Eddy Ball

The environmental health sciences community lost one of its distinguished senior members Dec. 9, 2009 with the unexpected death of former NIEHS and World Health Organization (WHO) scientist Thressa (Terri) Damstra, Ph.D., at age 67. Several of her friends and colleagues planned to join Damstra's family and personal friends in a celebration of her life on Jan. 30 in Chapel Hill, where she resided at the time of her death.

Damstra posed for this portrait in the mid-1990s toward the end of her tenure at NIEHS. (Archive photo courtesy of Steve McCaw)

In 2007, Damstra retired after serving as a senior staff member for the WHO International Programme on Chemical Safety International Research Unit working out of offices at NIEHS. Prior to that, she held several scientific and leadership positions at NIEHS during a tenure that lasted from 1973 to 1996. Under former NIEHS Directors David Rall, M.D., Ph.D., and Ken Olden, Ph.D., Damstra was a driving force in the Institute's global health initiatives and international partnerships (see text box).

When NIEHS/NTP Director Linda Birnbaum, Ph.D., learned of her former colleague's death, she wrote, "Terri had a love of life, a love of Science, and a love of NIEHS. She had a way of getting everyone to work together to achieve consensus, with everyone believing that's just what they wanted."

Asked about his experiences working with Damstra, long-time collaborator NIEHS Superfund Research Program Director William Suk, Ph.D., said, "I'm really going to miss her." Suk described Damstra as a "good friend [who] made things happen" and was capable of "putting researchers and investigators together in order to enhance the environmental health sciences worldwide," with a special impact on the health of children and women.

A native of Harkema, Friesland, in the Netherlands, Damstra immigrated to Grand Rapids, Mich. with her parents. She received a bachelor's degree from Calvin College and a Ph.D. in genetics from the University of Chicago. Damstra joined NIEHS following academic appointments at her alma mater and at the University of North Carolina at Chapel Hill.

Damstra is survived by daughter Amelia Entingh Pearsall, son-in-law Scott Pearsall, and two grandchildren of Woburn, Mass., as well as by four brothers and many nieces and nephews, all of Michigan.

Damstra at NIEHS

Damstra's interest in global health was nurtured early in her career at NIEHS when then-Director David Rall appointed her as the Institute's Special Assistant to the Director for International Programs. She came to the position from the NIEHS Office of Health Hazard Assessment where she had been involved in analyzing, reviewing, and evaluating scientific studies dealing with the potential health effects of environmental agents.

On behalf of the federal government, the NIEHS participated in a number of international agreements involving the exchange of official scientific visits and the transfer of scientific information and assistance. Nations with which formal agreements existed at the time included Great Britain, France, Egypt, Italy, West Germany, the U.S.S.R., and Japan. The Institute also participated in exchange visits with the People's Republic of China.

Damstra combined her commitment to global health with her interests in toxicology and endocrine disruption during the course of her NIEHS and WHO careers. Although she served as acting deputy director under Rall, Damstra readily returned to her role as an international coordinator of environmental health science research and translation.

When Damstra accepted her position with WHO, she recognized the support WHO continued to receive from NIEHS. "NIEHS was a major player in setting up this program," she said. She was also grateful that the Institute agreed to provide the program's lone Interregional Research Unit office space at NlEHS.

Damstra was active in the Federal Women's Program at NIEHS and her local community. Her professional memberships included the American Association for the Advancement of Science, the Society of Neuroscience, the Neurochemistry Society, and the Association for Women in Science.

(Archival research courtesy of NIEHS Reference/Inter-Library Loan Intern Kathryn Roth)

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Science Notebook

The Environment and T-cell Differentiation

By Robin Arnette

The Distinguished Lecturer for the month of January, Dan Littman, M.D., Ph.D., explained the contributions of several factors involved in the maturation of thymus-derived lymphocytes, also known as T-lymphocytes or T-cells, in a seminar titled "Role of Environmental and Intrinsic Factors in the Differentiation of Inflammatory T-cells." Laboratory of Respiratory Biology investigators Anton Jetten, Ph.D., and Donald Cook, Ph.D., co-hosted the Jan. 19 lecture.

Work by Littman on viral pathogenesis and T-cells has led to several major discoveries in immunology, but his presentation to the NIEHS community focused on the environmental factors that affect T-cell development.

Littman is currently the Helen L. and Martin S. Kimmel Professor of Molecular Immunology in the Departments of Pathology and Microbiology at the Skirball Institute Program of Molecular Pathogenesis at the New York University School of Medicine. (Photo courtesy of Steve McCaw)

Nuclear transcription factors in T-cell regulation and development

During Littman's research career, he devoted much of his efforts to understanding the involvement of ROR gamma t (RORγt) in T-cell lineage specification, particularly the differentiation of Th17 cells, a group of T-helper cells that have several functions. Although the main job of Th17 cells is to kill extracellular pathogens at mucosal barriers, they are also thought to be involved in tissue repair and, most importantly, associated with human autoimmune diseases and a variety of mouse inflammatory models. He said that he and his group accidently found the connection between RORγt and Th17 cells five years ago, but the timing was perfect since Th17 research was just beginning to heat up.

"Th17 cells make the cytokines [cellular signaling molecules] interleukin-17 (IL-17), IL-17F and IL-22 and become differentiated in the presence of IL-6 and transforming growth factor beta (TGF-β)," Littman explained. "However, work with one of our collaborators showed that rodent cells that lacked the nuclear receptor RORγt produced no IL-17, whereas cells with RORγt had an abundance of IL-17. Since onlyTh17 cells make IL-17, we knew there was a connection."

Co-host Anton Jetten, above, "is the only other person in the world who has the interest in RORgamma that we do," Littman joked. (Photo courtesy of Steve McCaw)

AhR and the immune system

According to Littman, although aryl hydrocarbon receptor (AhR) is not a nuclear receptor, it is still a ligand-regulated transcription factor. It is responsive to both natural and man-made environmental toxins such as dioxin. Other labs had reported that AhR had a role

in Th17 differentiation, and Littman's unpublished data suggested that when T-helper cells were differentiated to the Th17 lineage *in vitro*, AhR was also induced. AhR's induction level was similar to the induction of RORγt.

"Since some of our previous studies had demonstrated that the immune response gene forkhead box P3 (Foxp3) inhibited RORγt by binding to it," Littman argued, "we believe that AhR is required for induction of IL-22 and for clearance of potentially lethal intestinal pathogenic bacteria."

Some microbes fight off other bacterial infections

Littman said IL-22 drove the production of antimicrobial peptides that regulated the homeostasis of intestinal microflora, so his group became interested in studying the possible involvement of bacteria in Th17 cell differentiation.

When he treated recently-weaned mice with antibiotics, their intestinal Th17 cell count decreased. However, placing these mice in a cage with feces from mice that had not been treated caused their Th17 cell number to increase — showing there were differences in Th17 cell numbers according to the source of the mice.

"The mice purchased from Taconic Farms had lots of Th17 cells, but the same strain from Jackson Labs had very few," he said. A hybridization-based screen for DNA of all known bacteria determined that the Taconic Farms mice had *Segmented filamentous* bacteria (SFB) in their intestine, and further analysis determined that these mice also had increased amyloid A proteins in their intestine and high levels of IL-22 and IL-17 in their intestinal T-cells.

Littman concluded, "If you infect mice colonized with SFB with *Clostridium difficile* (*C. difficile*) an important hospital-acquired pathogen, we propose that the SFB would produce a signal through the amyloid A proteins, which would lead to the production of Th17 cells and eventually the making of IL-17 and IL-22. These two cytokines would release the antimicrobial peptides that would keep *C. difficile* in check."

Littman's goal is to find out if scientists can use bacteria or modulate RORγt activity to move the immune system away from susceptibility to infection and inflammatory processes.

Co-host Don Cook shares Littman's interests in T-cell differentiation, especially as it relates to the lung's immune responses to aeroallergens. (Photo courtesy of Steve McCaw)

With his interests in inflammation-related neurodegeneration of dopamine neurons, NIEHS Neuropharmacology Group Principal Investigator Jau-Shyong Hong, Ph.D., found much of interest in Littman's analysis of immune response signaling. (Photo courtesy of Steve McCaw)

NIEHS Visiting Fellow Yukimasa Takeda, Ph.D., above, is a member of Jetten's Cell Biology Group. (Photo courtesy of Steve McCaw)

Sitting with graduate students visiting from Duke University are NIEHS Principal Investigator Xiaoling Li, Ph.D., left, and Postdoctoral Fellow Xiumei Guo, Ph.D., of the Mammalian Aging Group. (Photo courtesy of Steve McCaw)

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Birnbaum Leads NIH Delegation

By Eddy Ball

NIEHS/NTP Director Linda Birnbaum, Ph.D., led a delegation of NIH scientists to the Joint Workshop on Environmental Pollution and Cancer in China and the U.S. held Jan 5–8 in Guangzhou, China. Birnbaum was the ranking member of the American delegation at the meeting jointly sponsored by the NIH and the Chinese Academy of Sciences (CAS) at the Guangzhou Institutes of Biomedicine and Health (GIBH), where she delivered closing remarks.

The carefully choreographed workshop balanced the American and Chinese research perspectives on the links between environmental pollution and cancer, with alternating talks by U.S. and Chinese researchers during each session of the meeting.

In her talk at the joint workshop, Birnbaum highlighted NIEHS/NTP as the world's premier environmental health sciences organization and placed research presented at the workshop clearly in the context of cancer as a complex disease influenced by the interaction of genetic and environmental factors. (Photo courtesy of CAS and Guangbiao Zhou, Ph.D.)

Closing presentations by Birnbaum, "Cancer and the Environment: Filling Knowledge Gaps Together," and GIBH Assistant Director General Assistant Donghai Wu, Ph.D., marked the culmination of three days of focused seminars and discussions by experts from the U.S. and China.

Addressing cancer as a complex disease

Tying together themes developed during the course of the meeting, Birnbaum offered participants an overview of research by NIEHS and NTP on cancer in such initiatives as the Agricultural Health Study, Sister Study, and NTP carcinogenesis assessment programs. She also offered participants a decidedly NIEHS perspective on the role that the intricate network of gene-environment interactions plays in the disease (see related Spotlight story).

Birnbaum argued that the traditional binary approach to disease — seeing genes and the environment as separate causes — "is an extreme oversimplification. Even in cases of 'genetic diseases,' such as cystic fibrosis, exposure is known to exacerbate symptoms," she explained, "and in 'environmental disease,' such as asbestosis, genetic susceptibility can influence disease severity."

Early in her talk, Birnbaum pointed to the "need to view the role of environment along the continuum from health to disease for individuals" with a better understanding of the "complex interactions" of genetic and molecular expression with the timing of exposures in determining health and disease outcomes as individuals age.

Birnbaum looked at advances in understanding the ways that early exposures can set the stage for later disease development through epigenetic modification of the human genome. She concluded her talk by looking to the future and urging her listeners to address the knowledge gaps she identified along the environment-cancer research continuum.

The workshop was one of more than 140 international seminars sponsored each year by CAS and its international partners, including NIH. CAS describes itself as "China's highest academic institution and national comprehensive R&D [research and development] center in natural sciences and high-tech innovation, [which] has always attached great importance to the academic exchange and cooperation with international science and technology communities."

Croyle spoke opposite CAS Deputy Director General Jinghua Cao, Ph.D., who welcomed workshop participants on behalf of the Chinese co-sponsor. Croyle is chair of the NIEHS Division of Extramural Research and Training director search committee. (Photo courtesy of NIH)

Samet gave the U.S. Keynote Address on Jan. 5. In 2008, he delivered a distinguished lecture at NIEHS on airborne particulate pollution. (Photo courtesy of Johns Hopkins University)

Buffler was honored in June 2009 for her lifetime achievement in leukemia research during an awards ceremony at the House of Lords in London. (Photo courtesy of Colin Hampden-White and CHILDREN with LEUKAEMIA)

Martin, a pulmonary medicine specialist, is a longtime advocate of NIH initiatives in global environmental health. (Photo courtesy of Steve McCaw)

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The NIH Delegation at Guangzhou

In addition to Birnbaum, who was the emissary of the NIH Office of the Director Francis Collins, M.D., Ph.D., NIH scientists from the NIEHS, National Cancer Institute (NCI), Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and Fogarty International Center (FIC) joined several NIH grantees in presenting the American perspective during workshop sessions on a broad range of environmental links to development and progression of cancer.

Several of the speakers have close ties to NIEHS. NCI Director of the Division of Cancer Control and Population Sciences Robert Croyle, Ph.D., gave the American-side's welcome remarks, and NIH grantee Jonathan Samet, M.D., of the University of Southern California, officially opened the meeting by speaking on behalf of U.S. scientists about "Challenges and Opportunities in Investigating Cancer and the Environment."

NIEHS grantee and University of California, Berkeley Professor Patricia Buffler, Ph.D., reported on her award-winning research on childhood cancers. NIEHS representative Bill Martin, M.D., of the Office of the Director, reviewed the topics of pathogenesis and therapeutics in U.S. clinical research.

Speaking on the last full day of the workshop on Jan. 7 were Joshua Rosenthal, Ph.D., deputy director of international training and research at FIC, and Britt Reid, D.D.S., chief of the Modifiable Risk Factors Branch and NCI. Rosenthal outlined NIH funding opportunities for collaborative research, while Reid explored the workings of the NIH grants process.

Kastner Kicks Off Clinical Seminar Series

By Laura Hall

"When the immune system turns against its host, it can be a horrific thing," said Daniel Kastner, M.D., Ph.D., as he explained how he and his colleagues tracked down the genetic and molecular causes of a series of rare autoinflammatory diseases that had puzzled doctors for years. Kastner's lively Jan. 22 presentation was the inaugural talk of the NIEHS Clinical Director's Seminar Series.

Kastner is the deputy director for Intramural Clinical Research for all of NIH as well as the clinical director and director of Translational Research for the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) Intramural Research Program. Acting Clinical Director Darryl Zeldin, M.D., hosted the seminar. Kastner began his presentation, titled "Horror Autoinflammaticus: The Expanding Spectrum of Systemic Autoinflammatory Diseases," with his experience trying to understand the causes of familial Mediterranean fever (FMF).

Kastner had patients with FMF, a disease characterized by recurrent episodes of painful inflammation in the abdomen, lungs, and joints, which is often accompanied by fevers and a rash. What puzzled doctors about

FMF and other similar inherited skin and bone inflammatory diseases was that the sporadic bouts of fevers and uncontrolled inflammation occurred throughout the body and mimicked infections and allergic conditions in their symptoms. However, the patients did not show any markers or evidence of infection, allergy, or immunodeficiency.

Knowing the disease was inherited, Kastner and his colleagues screened genes from FMF patients and their families searching for the disease gene and discovered the Mediterranean fever gene (*MEFV*), which encodes for the protein pyrin. Surprisingly, pyrin is involved in the innate immune system response to "danger" — pathogenic invaders like bacteria.

Unlike the adaptive immune response, which can "learn" to recognize and "remember" new sorts of invaders, the innate immune system recognizes a set repertoire of proteins from different kinds of pathogens. Pyrin is found in white blood cells, which go to the site of injury or disease to fight microbial invaders and help with tissue repair during the inflammatory response. The mutant pyrin proteins cause a much greater production of a pro-inflammatory cytokine, or chemical immune mediator, called interleukin-1 beta (IL-1ß) causing excessive inflammation.

FMF became the prototype for other similar disorders with episodes of seemingly unprovoked inflammation. Investigators found that deficiency of the IL-1 receptor antagonist (DIRA) and the cryopyrin-associated periodic syndromes (CAPS), such as neonatal-onset multisystem inflammatory disease (NOMID), were the result of genetic variants of the innate immune system.

Kastner, above, engaged the audience with the personal stories that his patients allowed him to share, including a poignant video of a mother and daughter discussing the toll that one of the inflammatory diseases had taken on their family. (Photo courtesy of Steve McCaw)

Host Darryl Zeldin, left, and NIEHS/NTP Director Linda Birnbaum, Ph.D., thought Kastner's seminar was interesting, informative, and also entertaining. (Photo courtesy of Steve McCaw)

Knowing the molecular basis for these diseases led to treatment options that, in some cases, actually prevented the disease symptoms. "Daniel Kastner gave us an excellent example of translational research in action when he spoke about his pioneering work on the genetic basis of systemic autoinflammatory diseases," said Zeldin. "It was an excellent start for our new Clinical Director's Seminar Series." NIEHS initiated the series as a follow up to the July 2009 ribbon cutting and clinical seminars celebrating the formal opening of its new Clinical Research Unit (see story).

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

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Pritchard Announces 2010 Intramural Research Awards

By Eddy Ball

On Jan. 19, NIEHS Acting Scientific Director John Pritchard, Ph.D., announced Intramural Research Awards (IRA) for two new collaborative initiatives by NIEHS principal investigators. Supported by Office of Director funds in fiscal year 2010, the awards go to teams of scientists in the Division of Intramural Research (DIR).

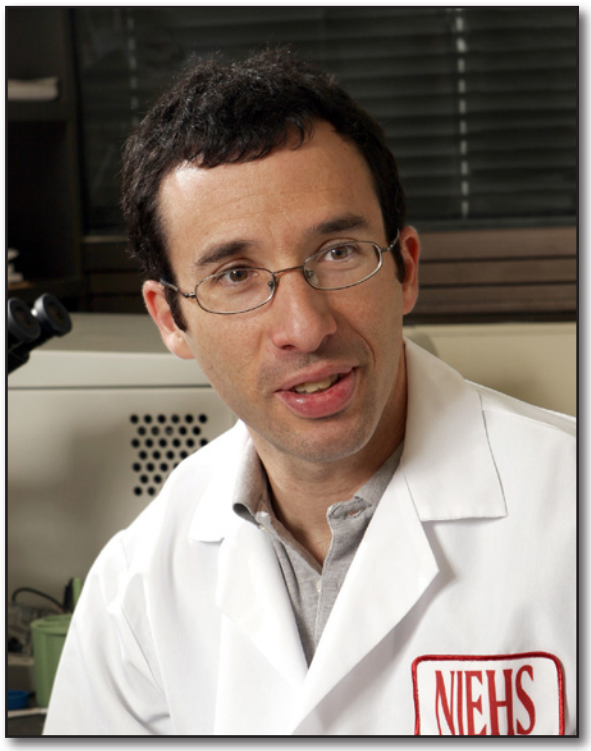
- Coupling of the innate immunity response, DNA damage, and p53 networks — Michael Fessler, M.D., of the Laboratory of Respiratory Biology (LRB) Host Defense Group; Stavros Garantziotis, M.D., of the LRB Matrix Biology Group; and Michael Resnick, Ph.D., of the Laboratory of Molecular Genetics Chromosome Stability Group

- SIRT1 dysfunction exaggerates neuroinflammation and accelerates microglia aging, causing progressive neurodegeneration — Jau-Shyong Hong, Ph.D., of the Laboratory of Pharmacology Neuropharmacology Group; and Xiaoling Li, Ph.D., of the Laboratory of Signal Transduction Mammalian Aging Group

When he announced the awards, Pritchard said of the awardees, "I think that the two proposals selected are truly outstanding examples of the kind of work we wish to stimulate with this program." Pritchard also congratulated all the applicants on the quality of their proposals and looked forward to supporting even more such efforts in coming years.

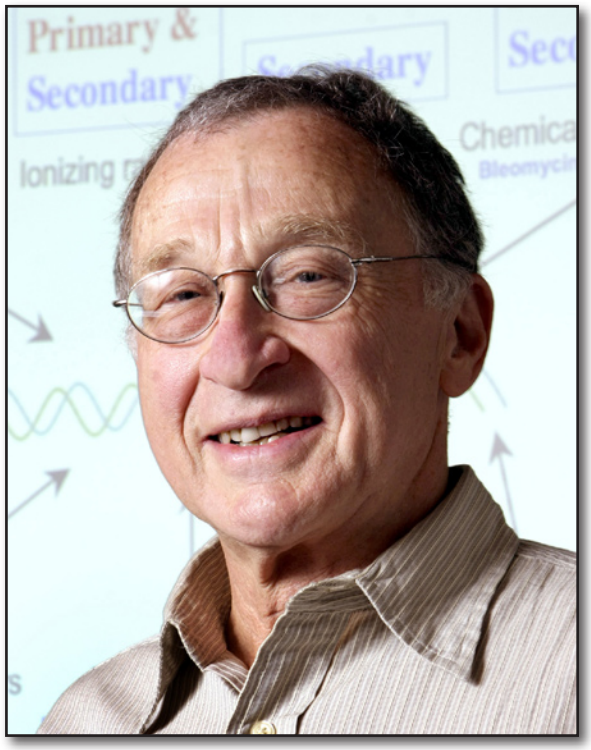
NIEHS solicited applications for these awards last October for peer review by DIR scientists Diane Forsythe, D.V.M., Traci M. T. Hall, Ph.D., Ken Korach, Ph.D., Thomas Kunkel, Ph.D., David Miller, Ph.D., and Darryl Zeldin, M.D. The IRA program recognizes the importance of facilitating the development of new collaborative and cross-disciplinary, cross-specialty initiatives by DIR investigators.

"Should our current tight budget be relieved as the final budget numbers become available," Prichard continued, "it is my hope that DIR will be able to fund an additional proposal with our own funds." (Photo courtesy of Steve McCaw)

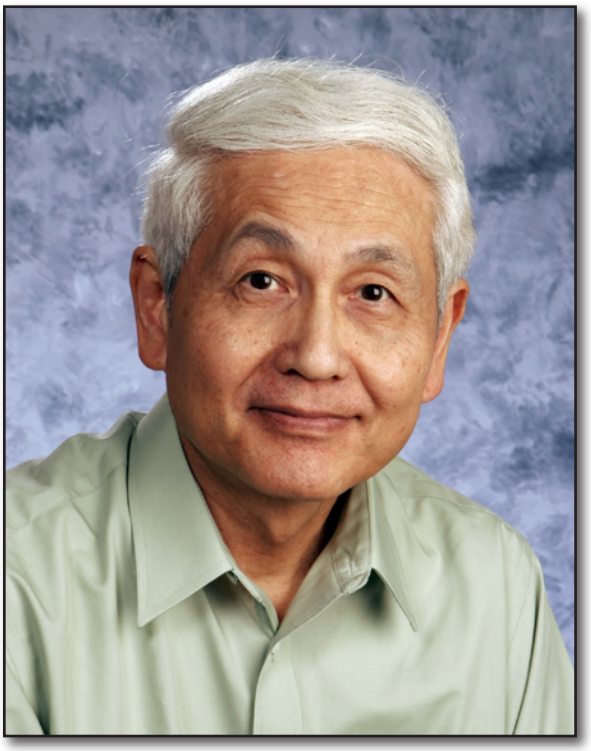


Fessler, above, received an Early Career Award at NIEHS Science Day 2008. He is also involved in research at the NIEHS Clinical Research Unit. (Photo courtesy of Steve McCaw)

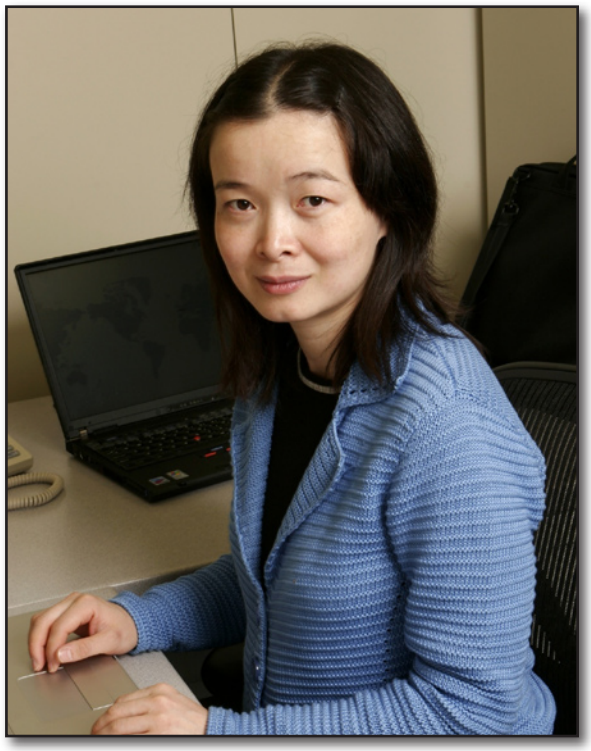
Garantziotis also conducts research at the NIEHS Clinical Research Unit, where he serves as staff clinician. (Photo courtesy of Steve McCaw)



In 2008, NIEHS honored Resnick as Scientist of the Year and as an author of the Paper of the Year. (Photo courtesy of Steve McCaw)



NIEHS trainees chose Hong Mentor of the Year in 2003. His research focuses on neurodegenerative diseases, such as Parkinson's. (Photo courtesy of Steve McCaw)



Li's January lecture at NIEHS is featured in this issue of the Environmental Factor. (Photo courtesy of Steve McCaw)

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Talk Highlights Utility of Copy Number Variant Studies

By Brian Chorley

In a Jan 11 guest lecture at NIEHS, Baylor College of Medicine Professor James Lupski, M.D., Ph.D., explored the clinical impact of copy number variants (CNVs) in the human genome. Lupski's talk on "Genomic Disorders: Mechanisms and Assays for CNV That Cause Human Disease" presented multiple examples of CNV association with disease and underscored the value of using state-of-the art CNV arrays for investigating genetically based disorders.

"Gene dosage is important to disease," Lupski explained, as he surveyed several examples in which deletion, duplication, or inversion of a genetic loci leads to clinically distinct disorders. (Photo courtesy of Steve McCaw)

In a diploid human genome, gene and non-coding DNA segments exist normally as two copies. Genomic rearrangement of these segments is caused by deletion, duplication, or inversion of the chromosomal DNA. As Lupski demonstrated, *de novo* genetic copy number variation — alterations occurring anew beyond primary sequence information — can have important implications for an individual's biology and health.

CNVs linked to human neurodegenerative disease

Lupski has studied CNVs for twenty years and first linked abnormal gene copy number to human disease while studying the neurodegenerative disease Charcot-Marie-Tooth type 1A (CMT1A) — a disease characterized by distal muscle loss and weakness and reduced sensation, such as touch and temperature. Lupski's research team found that chromosomal segment duplication was a cause of CMT1A, one of the most common genetically autosomal dominant disorders in humans.

Hosted by Visiting Fellow Shay Covo, Ph.D., above, a member of the NIEHS Chromosome Stability Group in the Laboratory of Molecular Genetics (LMG), the talk was the latest in the NIEHS Laboratory of Molecular Genetics Fellows Invited Lecture Series. (Photo courtesy of Steve McCaw)

Lupski noted, "76 to 90 percent of sporadic CMT1A patients have the duplication as a *de novo* event, so the mutations are happening quite frequently."

Study of CNVs in patients leads to better diagnosis and treatment

In the early 2000s, the human genome sequence was used by researchers to identify CNV hotspots. This information helped scientists develop clinical CNV assays that were quickly used to identify multiple novel deletion- or duplication-causative diseases in patients of various clinical phenotypes.

Specifically, two of these deletions were later linked to schizophrenia in two independent Nature publications. Lupski said that schizophrenia patients who harbored these deletions responded well to anti-psychotic drug

therapy. He was optimistic for the future clinical use of CNV assays "as ways to choose what drugs patients might respond better to, which is currently done by empirical trial-and-error methods" in complex diseases such as schizophrenia.

CNV-related mechanisms inform CNV assay design

Early clinical CNV arrays targeted approximately one hundred regions. Over a five-year period, the Baylor clinical diagnostic laboratory and Lupski's group significantly expanded the number of CNV targets to hundreds of regions interrogated by more than 180,000 oligonucleotides using better and cheaper technology, chromosome structural analyses, and CNV prediction (see text box). Predictions are based on identifying CNV hotspots that result from DNA recombination and replication mechanisms, which include non-allelic homologous recombination (NAHR), nonhomologous end joining (NHEJ), fork stalling and template switching (FoSTeS), and microhomology-mediated break-induced replication (MMBIR).

FoSTeS/MMBIR-mediated replication errors can result in exon drop out, or loss of one or more gene coding segments. However, Lupski noted that only about five percent of all genes have known functions. Interpreting the phenotypic effect of exon deletion is therefore limited, which reduces the number of informative targets on a clinical CNV assay.

In spite of these important advances, Lupski reminded his audience, current research leaves many questions unanswered — including which structural variations in the human genome are pathogenic and which benign, how frequently they occur, and what precisely are the molecular mechanisms involved in genomic rearrangements.

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

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Lupski's talk was well attended by NIEHS scientists. Shown above, right to left, are Staff Scientist Katarzyna Bebenek, Ph.D., Postdoctoral Fellow Michelle Heacock, Ph.D., Postdoctoral Fellow Jill Hesse, Ph.D., and Application Support Contractor Nick Staffa, Ph.D. (Photo courtesy of Steve McCaw)

LMG Laboratory Chief Jan Drake, Ph.D., above, was one of several LMG principal investigators who turned out to hear Lupski's talk. (Photo courtesy of Steve McCaw)

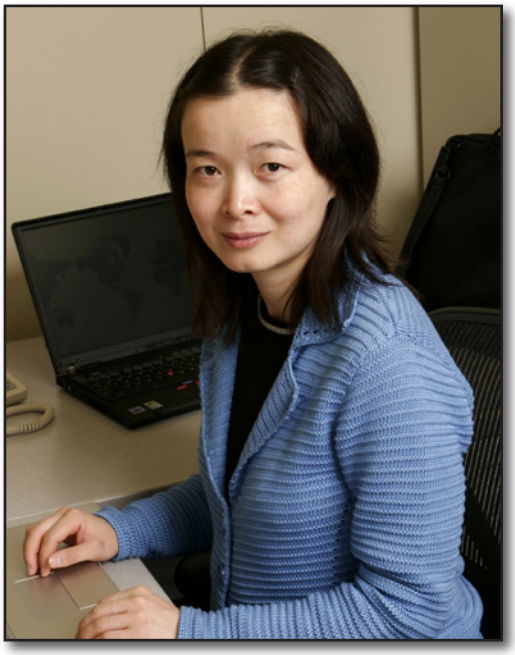
CNV Arrays versus Genome-Wide Association Studies

During his talk, Lupski argued for wider use of CNV arrays as opposed to genome-wide association studies (GWAS) for discovery of new genomic loci important to disease etiology. GWAS associate single-nucleotide polymorphisms (SNPs) with a phenotype or clinical manifestation. Lupski contends that assaying specific CNV loci enhances schizophrenia and autism identification in patients four-fold and at one percent of the cost of GWAS, based on data collected from 2008 and 2009 publications. Lupski summarized his argument poetically with the couplet, "SNPs SNPs SNPs so passé, CNVs are here to stay."

Researcher Looks for Key to Longevity

By Thaddeus Schug

"Aging is one certainty in life that we can all count on, but not one that is particularly well understood by the scientific community," observed Xiaoling Li, Ph.D., in her Jan. 7 talk at NIEHS. A principal investigator in the NIEHS Mammalian Aging Group, Li is hoping to shed light in this area of research by determining how environmental factors, such as nutrients, stresses, and hormones, impact the rate at which we age. Li presented some of her recent findings in a seminar titled "SIRT1 and Metabolic Diseases."

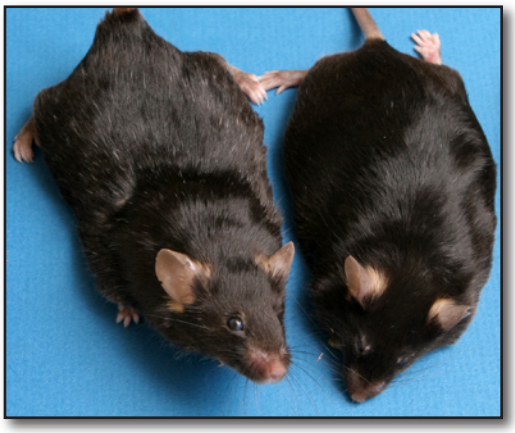


NIEHS Mammalian Aging Group Chief Xiaoling Li (Photo courtesy of Steve McCaw)

Li and her team study the sirtuin family of genes, which have been shown to extend the life span of yeast, worms, and flies in response to caloric restriction. The recent discovery that compounds such as resveratrol, a naturally occurring molecule found in the skin of grapes, activate sirtuins to extend lifespan has made headlines in popular television shows such as "60 Minutes" and in Newsweek magazine, noted event host Thomas Eling, Ph.D., a principal investigator in the NIEHS Laboratory of Molecular Carcinogenesis.

Looking at metabolism in SIRT1 knockout mice

Sirtuins are highly conserved NAD+-dependent protein deacetylases and/or ADP ribosyltransferases that function as master regulators of cellular metabolism. Li's research focuses primarily on SIRT1, which is the most conserved mammalian sirtuin. Knocking out SIRT1 completely in mice leads to severe developmental abnormalities and lethality, making it difficult to study the protein's true physiological functions. To bypass these issues, Li has created several tissue-specific SIRT1 knockout mouse models.



Although these two mice are the same age, consume the same diet, and live in identical conditions, the SIRT1 partial knockout (SIRT1 HET +/-) mouse, left, shows signs of premature aging, as evidenced by its dull, graying coat. The wild-type mouse (+/+), right, has a healthier, shinier coat. (Photo courtesy of Xiaoling Li)

Li first created a liver-specific SIRT1 knockout (LKO) mouse because SIRT1 activity is dependent on nutritional status and the liver is a central metabolic organ. Li has utilized this model to define a new role for SIRT1 as a key regulator of lipid metabolism. Her team discovered that when LKO mice consume a high-fat diet, they display defective fatty acid metabolism, show signs of liver inflammation, and have altered insulin signaling. These metabolic abnormalities are indicative of a condition called metabolic syndrome. Li noted that nearly one in four adults in the U. S. suffers from metabolic syndrome, and worldwide estimates are over 2.1 billion.

Using microarray technology, Li's team determined that SIRT1 interacts with and regulates the lipid sensing nuclear receptor called the peroxisome proliferators-activated receptor alpha (PPARα). PPARα signaling is responsible for regulating fatty acid metabolism. The researchers found that of 48 PPARα-regulated genes, 25 displayed lower expression in the knockout mouse livers. Li noted, "One mechanism by which SIRT1 regulates PPARα in the liver appears to be through PGC-1 — a key coactivator for PPAR and direct target of SIRT1." The study was recently published in the journal Cell Metabolism.

Li's group has found a similar metabolic profile in SIRT1 heterozygous mice challenged with a high-fat diet. These mice also have elevated steroid hormone levels and appear to age prematurely, which she demonstrated with a striking photograph comparing a heterozygous mouse to a liter-mate control.

Li concluded that gaining "a better understanding of the role of SIRT1 in specific tissues, will provide the molecular basis for development of novel anti-aging therapeutic targets."

Citation: Purushotham A, Schug TT, Xu Q, Surapureddi S, Guo X, Li X. 2009. Hepatocyte-specific deletion of SIRT1 alters fatty acid metabolism and results in hepatic steatosis and inflammation. Cell Metab 9(4):327-338. (See story)

(Thaddeus Schug, Ph.D., is a postdoctoral research fellow in the NIEHS Laboratory of Signal Transduction.)

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DNA Damage Found in Patients with Friedreich's Ataxia

By Ed Kang

An NIEHS/NIH-funded team of investigators published a groundbreaking study on gene expression and DNA damage among patients with the rare inherited disease Friedreich's ataxia (FRDA) in the Jan. 15 issue of PLoS Genetics. Their data – the 23 gene sets associated with a genotoxic stress response and the direct biological evidence of mitochondrial and nuclear DNA damage in the blood – result in the first genetic evidence-based working model of the disease (see text box).

Leading the 11-member team was former NIEHS Senior Investigator Ben Van Houten, Ph.D., who is now at the University of Pittsburgh Cancer Institute (UPCI).

Former NIEHS Senior Investigator and Program Analysis Branch Chief Ben Van Houten, above, is the Richard M. Cyert Professor of Molecular Oncology and leader of the molecular and cellular cancer biology program at UPCI, and professor, Department of Pharmacology and Chemical Biology, University of Pittsburgh School of Medicine. (Photo courtesy of Steve McCaw)

Too much of a good thing – FRDA leads to iron overload

"In FRDA, mutations in the gene frataxin reduce production of a protein that plays a role in keeping iron levels in balance within mitochondria," explained Van Houten. "Frataxin binds iron and helps build iron-sulfur clusters, which are important constituents of cellular proteins." The result is a significant reduction in mRNA and protein levels. Lead author Astrid Haugen, an NIEHS program analyst and biologist in Van Houten's NIEHS group, elaborated, "While iron is what allows blood cells to carry oxygen, too much iron is toxic to the body. Friedreich's ataxia leads to iron overload, setting the stage for cumulative DNA damage that eventually affects patients' nerve and muscle cells."

DNA damage: the key to understanding Friedreich's ataxia

The research team found direct evidence that FRDA patients accumulated significantly higher levels of mitochondrial and nuclear DNA damage as compared to controls. "We saw gene activity patterns that are associated with responses to DNA damage, and our comparisons and follow-up tests showed us that FRDA

patients have far more damage than seen in healthy people," said Van Houten. "We found gene expression signatures that correlated with frataxin levels, age of disease onset, and a standardized measure of patient disability."

Potential breakthroughs in biomarkers, therapies

For the study, the researchers profiled gene activity in blood samples from FRDA children and adults to search for biomarkers of the disease. Patients with prolonged frataxin deficiency display DNA damage detectable in peripheral blood, which may have predictive value in future clinical trials.

The study team expects the identification of potential biomarkers to help identify therapeutic approaches for this devastating disease. These biomarkers could be useful in assessing the current status of a patient's illness, as well as the response to experimental therapies in clinical trials. Also, new drug targets might be found in the DNA repair and iron-processing pathways affected by the lack of frataxin, generating much-needed treatment breakthroughs.

Even after moving into an administrative role in the NIEHS Division of Extramural Research and Training, Haugen maintained her scientific interest in gene expression analysis. (Photo courtesy of Steve McCaw)

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

Citation: Haugen AC, Di Prospero NA, Parker JS, Fannin RD, Chou J, Meyer JN, et al. 2010. Altered gene expression and DNA damage in peripheral blood cells from Friedreich's ataxia patients: cellular model of pathology. PLoS Genet 6(1): e1000812. doi:10.1371/journal.pgen.1000812

Friedreich's Ataxia

Named for German physician Nikolaus Friedreich (1825-1882), who first described the condition in the 1860s, Friedreich's ataxia is a rare, inherited disease that strikes about 1 in every 50,000 people in the United States. "Ataxia" refers to coordination problems that can range from unsteadiness to complete loss of motor control. Friedreich's ataxia is the most prevalent form of inherited ataxias, and it appears equally in males and females.

Infants with Friedreich's ataxia are outwardly normal at birth. However, as they grow into childhood and early adolescence, symptoms of the disease begin to appear. The disease initially affects the nervous system, leading first to an altered walking gait and later to speech problems and muscle problems as the damage to nerve tissue in the spinal cord and to nerves that control movement in the arms and legs becomes more severe. The disease is caused by a reduction of a critical iron homeostasis protein, frataxin, found in the mitochondria.

As Friedreich's ataxia progresses in patients, they may lose the muscle control necessary to speak, read or walk. Although the rate of progression of the disease varies, many patients are forced to use a wheelchair a decade or two after symptoms appear and eventually may become completely incapacitated. The most common cause of death is heart attack due to enlarged heart (hypertrophic cardiomyopathy), usually in middle age (mean age 38 years).

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Genetic Variation Influences Response to Environmental Exposure

By Omari J. Bandele

On Jan. 14, NIEHS grantee David Threadgill, Ph.D., explored "Preclinical Modeling of Environmental Exposures" during the latest installment of the NIEHS Keystone Science Lecture Series, hosted by Program Administrator David Balshaw, Ph.D. Threadgill's research focuses on understanding how genetic variations within the human population modulate response to environmental exposure and how to utilize new mouse strains that more closely approximate this modulation in laboratory experiments.

"We need to rethink the way experimental mouse models are used in order to better model the human population," Threadgill argued. "This will allow us to obtain more relevant information and improve our understanding of the human response to environmental exposure."

Threadgill spoke to a diverse group of scientists gathered in the Keystone conference room and, by a voice link, to scientists off-site. (Photo courtesy of Steve McCaw)

Expanding toxicology studies to include genetic variation

Early in his presentation, Threadgill, who is chair of the Department of Genetics at North Carolina State University, observed that most toxicological studies focus primarily on dose-response curves and other dose-based parameters, largely overlooking the contribution of genetic variation to the observed responses.

To address this shortcoming, Threadgill and colleagues in the Collaborative Cross project developed genetically diverse populations of mouse strains that capture variability across the entire mouse genome. He believes these mice will improve predictions of how human genetic variation modulates susceptibility to environmental risk factors. "Every human is a carrier of a specific genome, and that genome dictates how individuals respond to an environmental exposure," Threadgill explained. "We can synthetically model this in the laboratory."

Host David Balshaw, center, sat with colleagues from the NIEHS Division of Extramural Research and Training — sponsors of the Keystone Seminar Series. (Photo courtesy of Steve McCaw)

Threadgill highlighted the fact that the common inbred — genetically identical — mouse strains widely used as experimental models represent only 30% of the genetic variation known to exist in the mouse genome. This inherent limitation reduces the utility of these common inbred mouse strains in studies that examine the effect of genetic variation in a population.

Translating work with mosaic strains into potential applications with humans

The genetically diverse mouse models were generated by mating eight different inbred strains. This approach produced hundreds of mosaic strains, which represent 90% of the genetic variation found in mice and capture a large number of unique allele combinations not present in existing mouse models. According to Threadgill, these mosaics are better models for the human population. He believes they will allow investigators to interrogate genes in concert with environmental perturbations to examine the responses in an individual and a population.

Using this experimental model, Threadgill and colleagues demonstrated that the genetic makeup of mice influenced their propensity to exercise, as well as their clinical outcomes. Overall, physical activity correlated with weight loss. However, some outliers were highly active yet still gained weight — while others that were less active maintained or lost weight when provided the opportunity to exercise. Threadgill contends that novel allele combinations contributed to these unexpected cases and that this scenario may also occur in the human population.

A better understanding of genetic variation, Threadgill noted, could help scientists conducting clinical trials anticipate adverse reactions to drugs, as in the example mentioned in his slide, above. (Photo courtesy of Steve McCaw)

Threadgill believes variations in allele combinations contributed to the unexpected cases also seen in a study involving severe acute respiratory syndrome (SARS) and other infectious agents. In this study, lung function was used as an indicator of the level of sickness in the mice. Researchers found that as some strains lost weight during infection, the mice still had normal pulmonary pathology — while others showed the opposite pattern.

In conclusion, Threadgill provided examples of planned projects where the mosaic strains could aid in explaining clinical cases that may be influenced by human genetic diversity. One such study — through the Women's Health Initiative — involves the increased incidence of breast cancer observed in women on postmenopausal hormone replacement. Using his mouse models, Threadgill hopes to elucidate whether this phenomenon represents a general population risk or whether it is possible to identify a subset of women who are genetically susceptible to adverse effects from hormone replacement.

Biologist Stan Stasiewicz of the NIEHS Host Susceptibility Branch was one of several veteran bench scientists on hand to learn about Threadgill's work refining mouse strains to enhance extrapolation to human health. (Photo courtesy of Steve McCaw)

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

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This Month in EHP

By Eddy Ball

Environmental Health Perspectives (EHP) revisits lead this month in a feature article titled "Exposure on Tap: Drinking Water as an Overlooked Source of Lead," following up the December 2009 Focus. The article delves deeper into the issue by examining how public health officials react to the problem of potential exposure to lead through contaminated tap water, and discusses the role they can play in helping consumers prevent lead exposure through their tap water.

A companion story titled "Lead in Air: Adjusting to a New Standard" discusses a new petition under review by the U.S. Environmental Protection Agency to lower recently doubled monitoring threshold limits. The proposal has sparked debate over which contaminant source poses the greatest threat — industrial point sources or legacy contamination in soil from degraded house paint and gasoline.

Highlights of the issue include —

- Polyfluoroalkyl Chemicals and Cholesterol (NHANES 2003–2004)
- Peroxisome Proliferator–Activated Receptor Alpha (PPARα)-Dependent Effects of Diethylhexyl Phthalate (DEHP) on Energy Metabolism in Mice
- Childhood Asthma and Early-Life Exposure to Air Pollution

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Lippincott-Schwartz to Give 2010 Rodbell Lecture

By Eddy Ball

Jennifer Lippincott-Schwartz, Ph.D., will present the annual Rodbell Lecture on Feb. 9 at NIEHS with a talk on "Advances in Super-Resolution Imaging." The seminar begins at 2:00 p.m. with an introduction by NIEHS Transmembrane Signaling Group Principal Investigator and lecture host Lutz Birnbaumer, Ph.D.

Lippincott-Schwartz is the chief of the Section on Organelle Biology in the Cell Biology and Metabolism Branch at the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD).

Elected in 2008 to the National Academy of Sciences, Lippincott-Schwartz has applied the super-resolution imaging approaches she pioneered to make a succession of landmark discoveries across the field of cell physiology that are forcing a reassessment of many basic features of cellular processes. These include views on how compartments of the endomembrane system — such as the Golgi apparatus, nuclear envelope, peroxisomes, and autophagosomes — arise, as well as how they are maintained and operate.

Lippincott-Schwartz is the twelfth speaker in the annual lecture series honoring Nobel Laureate and former NIEHS Scientific Director Martin Rodbell, Ph.D. The first Rodbell Lecture featured Rodbell himself shortly before his death in 1998.

2010 Rodbell Lecturer Jennifer Lippincott-Schwartz participated in a 2008 Nature Methods video discussion of new developments in super-resolution imaging methods. (Photo courtesy of Jennifer Lippincott-Schwartz)

Advancing the Technique of Super-resolution Imaging

Lippincott-Schwartz's research has vastly expanded our understanding of the cell under healthy and diseased conditions by devising and applying innovative techniques to label, image, quantify, and model specific protein populations in living cells with green fluorescent protein (GFP) and track their fate over time. Her group is responsible for technical breakthroughs ranging from the introduction of confocal fluorescence recovery after photobleaching (FRAP) to the creation of a photoactivatable form of GFP that is invisible until activated by UV light, allowing unprecedented precision in quantifying and tracking protein populations.

The Lippincott-Schwartz lab also played a key role in developing the super-resolution imaging technique of photoactivated localization microscopy (PALM), which overcomes the diffraction barrier in fluorescence microscopy. PALM enabled imaging of genetically-expressed fluorescent proteins on the nanoscale of individual molecules for the first time.

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Kirk Smith to Speak at Duke

By Eddy Ball

Veteran NIEHS grantee Kirk Smith, Ph.D., will be at Duke University on Feb. 17 to present a seminar on global health that is open to the public free of charge. He will speak on "Incomplete Combustion—the Unfinished Global Agenda for Health, Environment and Climate Protection," from 4:30 to 6:00 p.m. in Perkins Library, Room 217, on the Duke campus. The Duke Global Health Institute is sponsoring the talk.

Smith is the director of the Global Health and Environment Program and a professor of Environmental Health Sciences at the University of California, Berkeley, where he holds the Maxwell Endowed Chair in Public Health. He is also founder and coordinator of the campus-wide Masters Program in Health, Environment, and Development. He was founder and head of the Energy Program of the East-West Center in Honolulu, where he still holds an appointment as adjunct senior fellow in Environment and Health. He is also a visiting senior scientist at the Woods Hole Research Center.

Smith, above, has also been honored for his academic accomplishments, which include appointments as chair of the Graduate Group in Environmental Health Sciences and the Brian and Jennifer Maxwell Endowed Chair in Public Health. (Photo courtesy of Kirk Smith and the Heinz Family Foundation)

His research work focuses on environmental and health issues in developing countries, particularly those related to health-damaging and climate-changing air pollution from energy production and use (see Planet Earth video interview). His research includes ongoing field measurements and health effects projects in India, Nepal, and Guatemala, as well as in China where he has worked since 1981.

Smith was one of the NIEHS speakers at a pre-Copenhagen 15 "Public Health Impacts of Reducing Greenhouse Gas Emissions" event Dec. 14, 2009 in Washington (watch video). A Dec. 21, 2009 New Yorker Annals of Invention article on heating and cooking stove technology for people in developing countries, "Hearth Surgery," featured Smith's pioneering work on the health effects of indoor air pollution.

Smith serves on a number of national and international scientific advisory and editorial boards, including those for the WHO Global Air Quality Guidelines and for the Global Energy Assessment, and he has published over 230 scientific articles and seven books. In 1997, was elected member of the US National Academy of Sciences, and in Sept. 2009, he received one of the 15th annual Heinz Awards, complete with a prize of $100,000.

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Extramural Papers of the Month

By Jerry Phelps

- Secrets of Drought Resistance Revealed
- Crystal Structure of Variant P450 Determined
- Lead Exposure Linked to Depression and Panic Disorders
- Genetic Risk Score for Multiple Sclerosis Developed

Read the current Superfund Research Program Research Brief. New issues are published on the first Wednesday of each month.

Secrets of Drought Resistance Revealed

A team of NIEHS-funded scientists has discovered the three-dimensional structure of abscisic acid, a plant hormone critical for drought survival, which helps to explain the mechanism behind drought tolerance in plants.

Drought resistant plants synthesize abscisic acid when they detect dry conditions, causing changes in all parts of the plants. Seeds lie dormant in the soil, leaf pores are closed to conserve water, and growth is slowed. Plants reprogram themselves for the sole purpose of surviving.

The research team made crystals of abscisic acid bound to its protein receptor called PYR1. Using x-ray crystallography, they determined the three-dimensional structure of the complex and found that PYR1 has an open space, akin to the inside of a tin can, where abscisic acid binds. As the binding occurs, a part of the protein called "the lid" is induced to close. Structural changes to other parts of PYR1 initiate binding with other proteins, triggering processes for drought resistance.

The authors suggest that chemicals mimicking the action of abscisic acid could be developed and sprayed on crops to protect them from droughts. It may also be possible to alter crops through selective breeding or genetic manipulation to produce more abscisic acid. According to government estimates, major droughts in the U.S. in the last three years alone have caused more than $10 billion in crop losses.

Citation: Nishimura N, Hitomi K, Arvai AS, Rambo RP, Hitomi C, Cutler SR, et al. 2009. Structural mechanism of abscisic acid binding and signaling by dimeric PYR1. Science 326(5958):1373-1379.

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Crystal Structure of Variant P450 Determined

An NIEHS grantee at the University of California, San Diego has determined the crystal structure of a genetic variant of cytochrome P450 2B6 in complex with its inhibitor. Structural insights such as this one are critical to understanding how enzymes bind to substrates and metabolize compounds, and how different genetic variations affect the enzyme's ability to initiate metabolism.

P450s are heme-containing monoxygenase enzymes. The multiple forms of cytochrome P450 metabolize a wide variety of endogenous and exogenous chemicals, including prostaglandins, steroids, drugs, and environmental chemicals. P450s interact with a variety of substrates, inhibitors, membrane lipids, and proteins that modulate their activity.

Genetic differences in the expression levels or activities of P450s are major determinants of individual responses to medications and environmental toxicants. This finding provides the first view of an important human enzyme that has been gaining in significance, as the list of compounds it interacts with has grown.

Citation: Gay SC, Shah MB, Talakad JC, Maekawa K, Roberts AG, Wilderman PR, et al. 2010. Crystal Structure of a Cytochrome P450 2B6 Genetic Variant in Complex with the Inhibitor 4-(4-Chlorophenyl)imidazole at 2.0 A Resolution. Mol Pharmacol doi 10:1124/mol.109.062570. [Epub ahead of print]

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Lead Exposure Linked to Depression and Panic Disorders

Young adults with elevated blood lead levels are more likely to have major depression and panic disorders, according to research supported by the NIEHS.

Lead is a well-known neurotoxicant causing behavioral and learning problems in children and young adults. It has also been associated with cognitive difficulties in older adults. It is ubiquitous and is found in air, soil, dust, and water. The elimination of lead from gasoline in the late 1970s has produced dramatic decreases in the average blood lead levels of children in the U.S.

Data were analyzed from 2000 participants of the National Health and Nutrition Examination Survey (NHANES) aged 20-29. The one-fifth of the participants with the highest blood lead levels (2.11 micrograms per deciliter) were 2.3 times more likely to have major depressive disorder and nearly five times more likely to have panic disorder than the one-fifth with the lowest blood lead levels (< 0.7 micrograms per deciliter) — levels considerably lower than the national average in the 1960s–1970s.

The authors point out that low-level lead exposure disrupts brain processes involving the neurotransmitters catecholamine and serotonin. Disruptions of these processes are known to be involved in depression and panic disorders, suggesting that exposure to lead in individuals predisposed to these conditions could trigger or worsen the severity of these disorders.

Citation: Bouchard MF, Bellinger DC, Weuve J, Matthews-Bellinger J, Gilman SE, Wright RO, et al. 2009. Blood lead levels and major depressive disorder, panic disorder, and generalized anxiety disorder in US young adults. Arch Gen Psychiatry 66(12):1313-1319.

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Genetic Risk Score for Multiple Sclerosis Developed

A large, multinational team of epidemiologists has developed a promising mathematical algorithm for predicting the likelihood of developing multiple sclerosis (MS). With additional refinement, it could become a useful tool in identifying people for early intervention or prevention efforts.

MS is a complex neurological disease, with an unknown origin, characterized by demyelination of the central nervous system, — affecting between 2 and 150 per 100,000 people. Recent genome-wide association studies have identified a number of genetic loci involved in MS, but there is still no clear understanding of the genetic

contribution to disease susceptibility. Environmental factors with convincing evidence of involvement with MS include sunshine, vitamin D, Epstein-Barr viral exposure, and smoking.

The current study employed a factor called the C statistic, which defines how well a model can differentiate between patients and controls. For clinical prediction, a C statistic of 0.8 or higher is considered useful.

In the current study involving 16 genetic loci associated with MS, the researchers used three different cohorts. The C statistics obtained ranged from 0.64 to 0.72, depending on whether gender, smoking history, and Epstein-Barr virus titers were incorporated. Although below the standard of 0.8, by incorporating other data and environmental factors, this study could lead to the development of a model that could identify individuals for early intervention efforts.

Citation: De Jager PL, Chibnik LB, Cui J, Reischl J, Lehr S, Simon KC, et al. 2009. Integration of genetic risk factors into a clinical algorithm for multiple sclerosis susceptibility: a weighted genetic risk score. Lancet Neurol 8(12):1111-1119.

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

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Intramural Papers of the Month

By Laura Hall and Omari Bandele

- Mapping RNA Polymerase II Stalling to Study Gene Regulation
- Store-Operated Calcium Entry Suppressed by Phosphorylated STIM1
- DNA Polymerase β and Poly (ADP-ribose) Polymerase Partner in DNA Base Excision Repair
- Genetic Studies Identify DNA Sequences Associated with Lung Function

Mapping RNA Polymerase II Stalling to Study Gene Regulation

Researchers from NIEHS and Virginia Commonwealth University have developed a high-resolution, high-throughput method to detect short RNAs derived from stalled RNA polymerase II (Pol II) in *Drosophila* cells and map them across the genome. The short RNAs are transcription products of Pol II promoter-proximal stalling in which an actively transcribing Pol II pauses or stalls 25-50 nucleotides downstream of the transcription start site.

Promoter-proximal stalling provides a way of controlling transcription output thereby regulating gene expression. The genome-wide study showed that promoter-proximal stalling is widespread with short RNAs, which are much shorter than complete transcripts, generated from over one-third of all genes — even highly active genes.

The nucleotide composition of the initially transcribed region determined the likelihood of Pol II stalling. Pol II pauses within a downstream region of weak RNA-DNA hybrid stability and then slides backward along the DNA to a site with thermodynamic stability and stalls.

These results indicate that polymerase recruitment to a promoter is not necessarily enough to automatically produce an entire transcript which would be made into a gene product. The efficiency of the early transcript elongation and how polymerase stalling duration is regulated is important for gene expression.

Citation: Nechaev S, Fargo DC, dos Santos G, Liu L, Gao Y, Adelman K. 2010. Global analysis of short RNAs reveals widespread promoter-proximal stalling and arrest of Pol II in *Drosophila*. Science 327(5963):335-338.

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Store-Operated Calcium Entry Suppressed by Phosphorylated STIM1

Cells use calcium ion or Ca (2+) levels as a component in some of their signaling networks that help coordinate and control cellular processes. NIEHS researchers examined the role of stromal interaction molecule 1 (STIM1), a Ca (2+) sensor protein, in the suppression of store-operated Ca (2+) entry (SOCE) in cells undergoing mitosis.

The researchers showed that phosphorylation of STIM1 at two sites — Serine 486 and Serine 668 — occurs specifically during mitosis and suppresses SOCE during cell division. Other STIM1 phosphorylation sites may also be involved.

Ca (2+) is an important second messenger — a signaling molecule that can be rapidly mobilized — and, in turn, can activate a signaling pathway that results in a cellular response. Cell Ca (2+) is mainly stored in intracellular storage organelles predominantly located in the endoplasmic reticulum (ER). These stored Ca (2+) levels are maintained by allowing extracellular Ca (2+) to influx into the cell by SOCE.

With Ca (2+) store depletion, STIM1 normally moves to spotted structures known as punctate in the ER very near the plasma membrane, a critical step in activating SOCE. The study showed that, due to STIM1 phosphorylation, this movement did not occur in mitotic cells thereby potentially protecting these cells from harmful Ca (2+) influx.

Citation: Smyth JT, Petranka JG, Boyles RR, DeHaven WI, Fukushima M, Johnson KL, et al. 2009. Phosphorylation of STIM1 underlies suppression of store-operated calcium entry during mitosis. Nat Cell Biol 11(12):1465-1472.

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DNA Polymerase ß and Poly (ADP-ribose) Polymerase Partner in DNA Base Excision Repair

Researchers from NIEHS have recently demonstrated that mouse fibroblast cells lacking either DNA polymerase β (Pol β) or poly (ADP-ribose) polymerase (PARP) activity display reductions in DNA base excision repair (BER). Published in the journal *DNA Repair*, the study provides the first direct evidence of the contribution of Pol β and PARP to BER in living cells.

BER is required to remove modified or abnormal bases that occur either spontaneously or by exposure to genotoxic agents. This DNA repair mechanism operates through two pathways, single-nucleotide (SN) and

multi-nucleotide or long-patch (LP). Using mouse fibroblast cells, Sam Wilson, M.D., and colleagues monitored SN-BER and LP-BER capacity on plasmids containing specific DNA lesions. The authors observed that the absence of Pol β or PARP activity reduced BER to similar levels, indicating that both polymerases function in the same repair pathway.

An advantage of this plasmid-based approach is it enables quantification of cellular BER capacity over time. Moreover, the experimental system may facilitate further comparisons of DNA repair in wild type and repair-deficient cells, and of the identification of inhibitors that alter repair capacity.

Citation: Masaoka A, Horton JK, Beard WA, Wilson SH. 2009. DNA polymerase beta and PARP activities in base excision repair in living cells. DNA Repair 8(11):1290-1299.

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Genetic Studies Identify DNA Sequences Associated with Lung Function

A collaborative research effort led by NIEHS scientists has identified genetic factors that increase the risk of impaired lung function. The study provides insight into the biological mechanisms that contribute to pulmonary function and possibly to the pathogenesis of chronic lung diseases — such as asthma and chronic obstructive pulmonary disease (COPD).

Stephanie London, M.D., and colleagues conducted analyses of data generated from several studies that involved over 20,000 participants. Using this data, the authors identified genetic variations in eight previously unrecognized DNA regions that alter lung function. Moreover, these DNA sequences contain genes with biological activities that may contribute to pulmonary function.

The investigators determined that individuals carrying the identified genetic variations have lower pulmonary function and are at greater risk for developing COPD. Moreover, predictions involving these genetic alterations were consistent with those for known risk factors associated with decreased lung function, such as smoking and increasing age.

The identification of specific DNA regions involved in impaired pulmonary activity encourages further studies to examine the biological mechanisms of how they contribute to lung function. Such studies may lead to new interventions to manage pulmonary diseases.

Citation: Hancock DB, Eijgelsheim M, Wilk JB, Gharib SA, Loehr LR, Marciante KD, et al. 2010. Meta-analyses of genome-wide association studies identify multiple loci associated with pulmonary function. Nat Genet 42(1):45-52.

(Laura Hall is a biologist in the NIEHS Laboratory of Pharmacology currently on detail as a writer for the Environmental Factor. Omari J. Bandele, Ph.D. is a postdoctoral fellow in the NIEHS Laboratory of Molecular Genetics Environmental Genomics Group.)

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NIEHS Papers of the Year 2009

By Laura Hall

Of the more than 2,700 papers published by NIEHS-supported researchers in 2009, 24 publications were chosen as Papers of the Year.

- Genome-Wide Association Study (GWAS) Identifies Multiple Loci Associated with Lung Function
- Genomic-Based Model Used to Predict Chemical Hepatocarcinogenicity
- Variations in Human Gut Microbiome Linked to Obesity
- Sun Exposure May Trigger Certain Autoimmune Diseases in Women
- Hexavalent Chromium in Drinking Water Causes Cancer in Rodents
- Clean Air Extends Life Expectancy
- Mapping RNA Polymerase II Stalling to Study Gene Regulation
- Skin Penetration Risk For Cadmium Selenide Nanomaterials Examined
- Surfactant Decreases Quenching in Brightly Fluorescent Single-Walled Nanotubes
- SIRT1 Identified as a Key Regulator of Hepatic Lipid Metabolism
- Genome-Wide Association Study Identifies Asthma Gene
- Calcium Signaling During Mitosis
- Genome-Wide Association Study Identifies Genes Increasing Heart Attack Risk
- DNA Scrunching During Gap Repair Synthesis
- Alzheimer's Disease Linked to Mitochondrial Damage
- Link Between Serum Cholesterol and Asthma
- Arsenic Compromises Immune Response
- Initiation of Repair of Random DNA Double Strand Breaks Requires RAD50
- Carbon Nanotubes Can Affect the Lung's Lining
- Hippocampal Synaptic Plasticity Can Be Modified by Differential Calcium Handling
- Electronic "Nose" Smells Toxins
- Female Mice Neonatally-Treated with Genistein Exhibit Reproductive Abnormalities
- Gene Variant Linked to Bladder Cancer
- Methoxyacetic Acid Disrupts Endogenous Estrogen Signaling

Genome-Wide Association Study (GWAS) Identifies Multiple Loci Associated with Lung Function

In GWAS studies, investigators search for specific locations in the genome sequence where variations can be associated with different observable traits such as diseases. NIEHS researchers directed a GWAS study to help understand the genetic basis of human lung development, asthma, and chronic obstructive pulmonary disease (COPD).

The study combined data from more than 20,000 participants from multiple studies and looked at two clinically important lung-function measures — forced expiratory volume and its ratio to forced vital capacity, an indication of airflow obstruction.

The analysis identified nine genetic loci associated with pulmonary function. Identifying these loci allow scientists to focus on these genes and determine how their interaction with environmental factors might cause disease.

Citation: Hancock DB, Eijgelsheim M, Wilk JB, Gharib SA, Loehr LR, Marciante KD, et al. 2010. Meta-analyses of genome-wide association studies identify multiple loci associated with pulmonary function. Nat Genet 42(1):45-52.

[Abstract] [Newsletter Article] [News Release]

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Genomic-Based Model Used to Predict Chemical Hepatocarcinogenicity

Of the estimated 30,000 chemicals in widespread commercial use in the U.S. and Canada, only a small fraction have been tested for carcinogenicity. The test for each chemical requires an expensive two-year bioassay followed by a scientific panel evaluation of its carcinogenic risk for humans.

NTP scientists developed a pattern recognition model that can identify hepatocarcinogens, based on the gene expression pattern of exposed animals, as an approach that allows prioritizing chemicals for testing. Using previously studied alkenylbenzenes, the model was able to correctly predict which were carcinogenic and the dose level that would cause carcinogenicity. The results showed that chemical exposure duration is a critical variable for the test.

Citation: Auerbach SS, Shah RR, Mav D, Smith CS, Walker NJ, Vallant MK, et al. 2009. Predicting the hepatocarcinogenic potential of alkenylbenzene flavoring agents using toxicogenomics and machine learning. Toxicol Appl Pharmacol Doi:10.1016/j.taap.2009.11.021. [Epub ahead of print] [Abstract]

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Variations in Human Gut Microbiome Linked to Obesity

The human gut microbiome, which helps in digesting food, is made up of the microbial community, their genes, and their gut interactions. A study of the gut microbiome of lean and obese adult female twins and their mothers revealed that obesity was associated with lower numbers and different phyla of bacteria, and increases in bacterial genes that extract calories from food and process nutrients.

The results showed that the microbial community makeup varied between individuals, but that family members had very similar communities compared to unrelated individuals. The microbial genes present were sufficiently shared to identify a core microbiome of genes amongst the subjects.

Citation: Turnbaugh PJ, Hamady M, Yatsunenko T, Cantarel BL, Duncan A, Ley RE, et al. 2009. A core gut microbiome in obese and lean twins. Nature 457(7228):480-484. [Abstract] [Synopsis]

Supported by NIEHS grant P50ES012742, John Stegeman, Ph.D., Woods Hole Oceanographic Institute.

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Sun Exposure May Trigger Certain Autoimmune Diseases in Women

Dermatomyositis is an autoimmune muscle disease that weakens the muscles and causes distinctive rashes. NIEHS researchers collaborated with myositis centers across the country to determine if ultraviolet (UV) radiation from sunlight was associated with the development of dermatomyositis.

They found an association between UV radiation intensity and the proportion of patients with dermatomyositis and with the proportion of patients expressing myositis antibodies, anti-Mi-2 autoantibodies. The data suggest that sex influences the effects of UV radiation on autoimmune disorders because the associations were only found in women.

Citation: Love LA, Weinberg CR, McConnaughey DR, Oddis CV, Medsger TA Jr, Reveille JD, et al. 2009. Ultraviolet radiation intensity predicts the relative distribution of dermatomyositis and anti-Mi-2 autoantibodies in women. Arthritis Rheum 60(8):2499-2504. [Abstract] [Synopsis] [News Release]

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Hexavalent Chromium in Drinking Water Causes Cancer in Rodents

Detectable levels of hexavalent chromium (Cr(VI)), an industrial chemical, has been reported in approximately 30 percent of the drinking water sources monitored in California. Cr(VI) is known to be carcinogenic to humans after inhalation exposure, but the effects from chronic oral exposure to Cr(VI) is unknown.

NTP scientists characterized the chronic oral toxicity and carcinogenicity of Cr(VI) in rats and mice, with a two-year drinking water study of sodium dichromate dihydrate (SDD). SDD is widely used in industry to produce chromium compounds. The exposed animals developed abnormal growths in the oral cavity and small intestine, providing clear evidence of carcinogenicity.

Citation: Stout MD, Herbert RA, Kissling GE, Collins BJ, Travlos GS, Witt KL, et al. 2009. Hexavalent chromium is carcinogenic to F344/N rats and B6C3F1 mice after chronic oral exposure. Environ Health Perspect 117(5):716-722. [Article] [NTP Factsheet]

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Clean Air Extends Life Expectancy

Particulate matter in the air, such as from combustion by-products, can be inhaled into the lungs and cause heart and lung disease and, potentially, increased mortality. Researchers examined the association of exposure to 2.5 micrometer or less sized particulate matter (PM 2.5) pollution and life expectancy, in 51 metropolitan areas throughout the U.S. between 1980 and 2000.

They found that a decrease in 10 micrograms per cubic meter in the concentration of fine-particulate matter was associated with an estimated increase in mean life expectancy of 0.61 years. The scientists concluded that reducing ambient fine-particulate air pollution contributed to significant and measurable increases in life expectancy in the U.S.

Citation: Pope CA 3rd, Ezzati M, Dockery DW. 2009. Fine-particulate air pollution and life expectancy in the United States. N Engl J Med 360(4):376-386. [Abstract] [Synopsis]

Supported by NIEHS grant P30ES000002, Douglas Dockery, Sc.D., Harvard School of Public Health.

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Mapping RNA Polymerase II Stalling to Study Gene Regulation

Contrary to the common belief that the recruitment of RNA polymerase II (Pol II) to a promoter is sufficient for gene activation and transcript elongation, a recent study has shown that promoter-proximal stalling, whereby Pol II accumulates at promoters and stalls, is widespread. Scientists from NIEHS and Virginia Commonwealth University developed a method to detect short RNAs derived from stalled Pol II in *Drosophila* cells and mapped them across the genome to determine where stalling occurred.

The research team showed that the sequence composition of initially transcribed regions is important in polymerase stalling. The results indicate that promoter-proximal stalling, which occurs in over one-third of all genes, provides a way of controlling transcription output thereby regulating gene expression.

Citation: Nechaev S, Fargo DC, dos Santos G, Liu L, Gao Y, Adelman K. 2010. Global analysis of short RNAs reveals widespread promoter-proximal stalling and arrest of Pol II in Drosophila. Science 327(5963):335-338 [epub ahead of press] doi. 10.1126/science.1181421. [Abstract] [Synopsis]

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Skin Penetration Risk for Cadmium Selenide Nanomaterials Examined

Nanoscale materials, which are reported to be in many cosmetics, sunscreens, and other consumer products, can potentially cross the skin and enter the body — possibly causing harm.

To evaluate the risk of transdermal absorption, National Toxicology Program (NTP) scientists evaluated the penetration of polyethylene glycol-coated cadmium selenide core quantum dots (QD) into mouse skin, by monitoring internal sentinel organs — liver and regional draining lymph nodes. The QD nanoscale material was applied to mouse skin in a cream, similar to those used in skin lotions and sunscreens.

The study results showed no QD penetration occurred in mice with intact skin, but in mice with dermabraded skin, the QD levels in the sentinel organs were elevated.

Citation: Gopee NV, Roberts DW, Webb P, Cozart CR, Siitonen PH, Latendresse JR, et al. 2009. Quantitative determination of skin penetration of PEG-coated CdSe quantum dots in dermabraded but not intact SKH-1 hairless mouse skin. Toxicol Sci 111(1):37-48. [Abstract]

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Surfactant Decreases Quenching in Brightly Fluorescent Single-Walled Nanotubes

NIEHS-supported chemists discovered a way to increase the light-emitting efficiency of single-walled carbon nanotubes (SWNTs) as high as 20 percent.

Photoluminescent properties — whereby light is emitted after light units called photons are absorbed — make SWNTs potentially useful for optoelectronics, medical imaging, and sensing. However, the emission of light, or luminescence, can be reduced or quenched when oxygen settles on, and then binds to, the SWNT surface.

The researchers used a surfactant chemical derived from vitamin B-12 to coat the nanotubes. This coating prevents oxygen from binding to the SWNTs and helps prevent SWNT aggregation that can also reduce luminescence.

Citation: Ju SY, Kopcha WP, Papadimitrakopoulos F. 2009. Brightly fluorescent single-walled carbon nanotubes via an oxygen-excluding surfactant organization. Science 323(5919):1319-1323. [Abstract] [Synopsis]

Supported by NIEHS grant R01ES013557, James Rusling, Ph.D., University of Connecticut.

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SIRT1 Identified as a Key Regulator of Hepatic Lipid Metabolism

Sirtuin 1 (SIRT1) is an important regulator of energy homeostasis, in response to nutrient availability in many metabolic pathways and tissues. NIEHS scientists showed that in the liver, SIRT1 regulates lipid metabolism, particularly fatty acid metabolism, by positively regulating peroxisome proliferator-activated receptor alpha (PPARα).

PPARα is a nuclear receptor that functions as a lipid sensor and activates genes metabolizing fatty acids. Overexpression of SIRT1 stimulated PPARα signaling. Liver-specific SIRT1 knockout mice had impaired PPARα signaling and developed fatty liver, inflammation, and endoplasmic reticulum stress, after a high fat diet. Thus, SIRT1 may be a therapeutic target for prevention of obesity-associated metabolic diseases.

Citation: Purushotham A, Schug TT, Xu Q, Surapureddi S, Guo X, Li X. 2009. Hepatocyte-specific deletion of SIRT1 alters fatty acid metabolism and results in hepatic steatosis and inflammation. Cell Metab 9(4):327-338. [Abstract] [Synopsis] [Newsletter Article]

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Genome-Wide Association Study Identifies Asthma Gene

Asthma is a complex chronic airway disease that affects more than 20 million Americans and 300 million people worldwide. A multicenter genome-wide association (GWA) analysis identified the phosphodiesterase 4D (PDE4D) gene as an asthma susceptibility gene.

Two PDE4D single nucleotide polymorphisms (SNPs) were significantly associated with asthma. PDE4D is involved in controlling airway smooth muscle contraction. Phosphodiesterase inhibitors are used to treat asthma. Studying the PDE4D SNPs can lead to a better understanding of how PDE4D is involved in asthma and how PDE4D inhibitors work.

Citation: Himes BE, Hunninghake GM, Baurley JW, Rafaels NM, Sleiman P, Strachan DP, et al. 2009. Genome-wide association analysis identifies PDE4D as an asthma-susceptibility gene. Am J Hum Genet 84(5):581-593. [Abstract] [Synopsis]

Supported by NIEHS grants P01ES011627 and P30ES007048, Frank Gilliland, M.D., Ph.D., University of Southern California.

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Calcium Signaling During Mitosis

Cells use calcium ion (Ca2+) levels as a component in some of their signaling networks that help coordinate and control cellular processes. NIEHS scientists showed that phosphorylation of stromal interaction molecule 1 (STIM1), a Ca2+ sensor protein, occurs specifically during mitosis and suppresses store-operated Ca2+ entry (SOCE).

With Ca2+ store depletion, STIM1 normally moves to spot-like structures in the ER near the plasma membrane, a critical step in activating SOCE. The study showed that, due to STIM1 phosphorylation, this movement did not occur in mitotic cells thereby potentially protecting these cells from harmful Ca2+ influx.

Citation: Smyth JT, Petranka JG, Boyles RR, DeHaven WI, Fukushima M, Johnson KL, et al. 2009. Phosphorylation of STIM1 underlies suppression of store-operated calcium entry during mitosis. Nat Cell Biol 11(12):1465-1472. [Abstract] [Synopsis] [Newsletter Article]

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Genome-Wide Association Study Identifies Genes Increasing Heart Attack Risk

Myocardial infarction (MI), or heart attack, is a leading cause of death and disability worldwide. MI is a heritable disease with inherited genes having a greater impact on early-onset MI — heart attacks in men 50 or women 60 years old or younger.

The Myocardial Infarction Genetics Consortium (MIGC) conducted a genome-wide association study that identified nine single nucleotide polymorphisms (SNPs) associated with early-onset MI — three of the SNPs are newly identified. The MIGC also tested copy number variants, but did not find any association between the number of specific gene copies in an individual's genes and risk of early-onset MI.

Citation: Myocardial Infarction Genetics Consortium. 2009. Genome-wide association of early-onset myocardial infarction with single nucleotide polymorphisms and copy number variants. Nat Genet 41(3): 334-341. [Abstract] [Synopsis]

Supported by NIEHS grant P30ES007033, David Eaton, University of Washington.

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DNA Scrunching During Gap Repair Synthesis

Normal metabolic activities and environmental exposures, such as UV light, can cause structural damage to DNA and mutations. Polymerase lambda (Pol λ), a DNA repair enzyme, can fill in short gaps of 1–6 missing nucleotides (nt) in damaged DNA. DNA binding and gap filling are well characterized for 1 nt gaps, but the location of yet-to-be copied template nucleotides in longer gaps is unknown.

NIEHS scientists, collaborating with investigators at the University of North Carolina at Chapel Hill and Stony Brook University in New York, determined crystal structures showing that, when bound to a 2- nt gap, Pol λ scrunches the template strand and binds the additional yet-to-be-copied template base in an extrahelical position within a binding pocket that comprises three conserved amino acids.

This study sheds light on the specific structural changes necessary during DNA repair and, ultimately, the protection against mutations due to environmental exposures.

Citation: Garcia-Diaz M, Bebenek K, Larrea AA, Havener JM, Perera L, Krahn JM, et al. 2009. Template strand scrunching during DNA gap repair synthesis by human polymerase lambda. Nat Struct Mol Biol 16(9):967-972. [Abstract] [Synopsis]

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Alzheimer's Disease Linked to Mitochondrial Damage

Alzheimer's disease (AD) is a progressive and fatal brain disease, characterized by damage and death of neurons, that has no current cure. A new study on a mitochondrial protein, dynamin-related protein 1 (Drp1), suggests that Drp1 could be a new drug target to reduce or even prevent neurodegeneration in Alzheimer's patients.

The researchers found that Drp1 is S-nitrosylated by nitric oxide, whereby the oxygen of nitric oxide binds to a sulfur in Drp1 in response to oligomers of beta-amyloid — a protein considered a key mediator in AD — causing neuronal mitochondrial and synaptic damage like that seen in AD.

Citation: Cho DH, Nakamura T, Fang J, Cieplak P, Godzik A, Gu Z, Lipton SA. 2009. S-nitrosylation of Drp1 mediates beta-amyloid-related mitochondrial fission and neuronal injury. Science 324(5923):102-105. [Abstract] [Synopsis]

Supported by NIEHS grant P01ES016738, Stuart Lipton, M.D., Ph.D., Burnham Institute for Medical Research.

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Link Between Serum Cholesterol and Asthma

Cholesterol has complex effects on inflammation, but its effects on asthma, an inflammatory airway disease, is unknown. NIEHS scientists collaborated with investigators at SRA International, Inc. and Rho Federal Systems Division, Inc. to determine relationships between levels of three serum cholesterol measures and asthma or wheeze in a sample of 7005 participants that was representative of the U.S. population.

High-density lipoprotein cholesterol was not different in patients with or without current asthma. However, asthma was inversely related to serum total cholesterol and non-high-density lipoprotein cholesterol chiefly reflecting a relationship among Mexican Americans. These results may explain why Mexican Americans have the lowest prevalence of asthma in the country, despite increased asthma risk factors.

Citation: Fessler MB, Massing MW, Spruell B, Jaramillo R, Draper DW, Madenspacher JH, et al. 2009. Novel relationship of serum cholesterol with asthma and wheeze in the United States. J Allergy Clin Immunol 124(5):967-974. [Abstract] [Newsletter Article]

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Arsenic Compromises Immune Response

As many as 25 million Americans and hundreds of millions of people worldwide are exposed to arsenic in their drinking water.

A new study demonstrated that a five-week exposure to a low dose of 100 parts per billion of arsenic in drinking water significantly compromised the immune response to respiratory influenza A (H1N1) in mice.

The researchers hypothesized that chronic arsenic exposure could contribute to increased lung disease risk in humans. They also suggested that in areas like Southeast Asia and Mexico that have very high levels of arsenic in drinking water, the impact of a pandemic strain of influenza could be enhanced.

Citation: Kozul CD, Ely KH, Enelow RI, Hamilton JW. 2009. Low dose arsenic compromises the immune response to influenza A infection *in vivo*. Environ Health Perspect 117(9):1441-1447. [Abstract]

Supported by NIEHS grant P42ES007373,Bruce Stanton, Ph.D., Dartmouth Medical School.

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Initiation of Repair of Random DNA Double-Strand Breaks Requires RAD50

Little is known about how cells repair random DNA double-strand breaks (DSBs), such as those caused by gamma radiation, a therapy commonly used in cancer treatment. NIEHS researchers and an Indiana University-Purdue University Indianapolis collaborator found a way to track early events in repairing DSBs caused by gamma irradiation in yeast using pulsed field gel electrophoresis (PFGE).

The investigators demonstrated that the initial step in repair of random DSBs involved resection, the removal of one of the strands at a DSB end, and that this step depends on the MRX complex composed of the proteins Mre11, Rad50, and Xrs2. Yeast lacking Rad50 or Mre11 were slow in generating resected ends, a key step in DSB repair.

Citation: Westmoreland J, Ma W, Yan Y, Van Hulle K, Malkova A, Resnick MA. 2009. RAD50 is required for efficient initiation of resection and recombinational repair at random, gamma-Induced double-strand break ends. PLoS Genet 5(9):e1000656. [Abstract] [Synopsis]

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Carbon Nanotubes Can Affect the Lung's Lining

Carbon nanotubes (CNTs), present in many products, are similar to asbestos in that they are fiber-shaped. It is unknown if CNTs are comparable to asbestos in causing lung disease in humans, such as lung tissue scarring and mesothelioma, and cancer of the pleura.

Researchers found that multiwalled CNTs (MWCNTs) reach the subpleura, the lining of the lung, in mice exposed to one single six hour inhalation of 30 milligrams per cubic meter of MWCNTs, causing the accumulation of immune cells at the pleural surface within the first day and lung scarring after two weeks.

Asbestos exposure also results in subpleural scarring suggesting that individuals with occupational MWCNT inhalation exposure could be at risk for lung disease.

Citation: Ryman-Rasmussen JP, Cesta MF, Brody AR, Shipley-Phillips JK, Everitt JI,Tewksbury EW, et al. 2009. Inhaled carbon nanotubes reach the subpleural tissue in mice. Nat Nanotechnol 4(11):747-751. [Abstract] [Synopsis] [Newsletter Article]

Supported by NIEHS grant R21ES015801, James Bonner, Ph.D., North Carolina State University.

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Hippocampal Synaptic Plasticity Can Be Modified by Differential Calcium Handling

Scientists at the NIEHS and Duke University examined neurons from different subareas — CA1, CA2, and CA3 — of the hippocampus, a brain area involved in memory formation, to understand the mechanisms underlying synaptic plasticity, as measured by long-term potentiation (LTP).

The scientists showed that CA2 neurons, which do not reliably display LTP, have lower postsynaptic calcium ion (Ca2+) concentrations due to Ca2+ buffering and higher rates of Ca2+ extrusion, when compared to CA1 and CA2. The results indicate that CA2 neurons have the cellular machinery required for plasticity, but the expression is modulated by Ca2+ handling. Other brain regions may have this same modulation.

Citation: Simons SB, Escobedo Y, Yasuda R, Dudek SM. 2009. Regional differences in hippocampal calcium handling provide a cellular mechanism for limiting plasticity. Proc Natl Acad Sci USA 106(33):14080-14084. [Abstract] [Synopsis]

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Electronic "Nose" Smells Toxins

Scientists have developed a postage stamp- sized sensor that can rapidly detect and identify poisonous gases with an array of pigmented dots that displays a different color pattern, or fingerprint, specific to each gas.

The researchers tested their sensor with 19 diverse toxic industrial chemicals that can be dangerous to life or health, including ammonia, chlorine, and sulfur dioxide. The sensor was able to accurately identify each chemical, usually well below their permissible exposure limit concentrations, within seconds to two minutes.

Security, as well as occupational exposure monitoring, has an immediate need for the sensor's ability to rapidly identify and quantify a wide variety of toxic gases.

Citation: Lim SH, Feng L, Kemling JW, Musto CH, Suslick KS.2009. An optoelectronic nose for the detection of toxic gases. Nat Chem 1:562-567. [Abstract] [Synopsis] [Newsletter Article] [News Release]

Supported by NIEHS grant U01ES016011, Kenneth Suslick, Ph.D., University of Illinois at Urbana-Champaign.

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Female Mice Neonatally Treated with Genistein Exhibit Reproductive Abnormalities

The phytoestrogen genistein is a naturally occurring estrogenic chemical found in soy and soy-based infant formulas. Female mice treated neonatally with genistein have multioocyte follicles, lack regular estrous cyclicity, and are infertile even after superovulation.

NIEHS investigators studied oocyte developmental competence and timing of embryo loss in genistein-exposed mice, to determine the cause of their infertility. The scientists found that mice neonatally treated with genistein developed competent oocytes, but because genistein exposure produced an abnormal oviductal environment, the oocytes were unable to implant in the uterus, leading to reproductive failure.

Citation: Jefferson WN, Padilla-Banks E, Goulding EH, Lao SP, Newbold RR, Williams CJ. 2009. Neonatal exposure to genistein disrupts ability of female mouse reproductive tract to support preimplantation embryo development and implantation. Biol Reprod 80(3):425-431. [Abstract] [Synopsis]

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Gene Variant Linked to Bladder Cancer

In the U.S., bladder cancer is the fourth most common cancer in men. In a genome-wide association study, scientists have discovered a new susceptibility gene for bladder cancer in the U.S. and European populations — a gene variant of the prostate stem cell antigen (*PSCA*) gene.

One nucleotide difference in the gene variant alters the starting point of transcription and results in the deletion of nine amino acids in the N-terminal localization sequence of the protein that directs the unprocessed protein to modification sites. The gene variation significantly reduces promoter activity, making protein synthesis less efficient. The *PSCA* variant is common in U.S. and European populations.

Citation: Wu X, Ye Y, Kiemeney LA, Sulem P, Rafnar T, Matullo G, et al. 2009. Genetic variation in the prostate stem cell antigen gene PSCA confers susceptibility to urinary bladder cancer. Nat Genet 41(9):991-995. [Abstract] [Synopsis]

Supported by NIEHS grant P42ES007373, Bruce Stanton, Ph.D., Dartmouth Medical School.

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Methoxyacetic Acid Disrupts Endogenous Estrogen Signaling

Exposure from both ethylene glycol monomethyl ether (EGME), an industrial solvent, and its primary metabolite, methoxyacetic acid (MAA), has been linked to reproductive toxicity in epidemiology studies. NIEHS scientists and a collaborator from the German Cancer Research Center evaluated the mechanistic effects of MAA on estrogen receptor (ER) expression and estrogen signaling.

MAA activated the cytomegalovirus promoter to stimulate exogenous ER expression in an *in vitro* system. In contrast, MAA decreased endogenous ERα expression and attenuated 17ß-estradiol-stimulated endogenous gene expression in MCF-7 cells and mouse uterus. The results suggest that EGME and MAA toxic effects may be due, at least in part, to attenuation of endogenous ER-mediated signaling.

Citation: Henley D V, Mueller S, Korach KS. 2009. The short-chain fatty acid methoxyacetic acid disrupts endogenous estrogen receptor-α-mediated signaling. Environ Health Perspect 117(11):1702-1706. [Abstract] [Synopsis]

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

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Inside the Institute

Wright Wraps Career as Information Guru

By Eddy Ball

NIEHS Biomedical Librarian Larry Wright, Ph.D., bid farewell to friends and colleagues on a familiar note at a retirement reception in the NIEHS Library on Dec. 30. As well-wishers dropped by to reminisce and talk about his retirement plans, Wright couldn't resist getting in a final word about the value of the specialized library at NIEHS for the scientists who work here and throughout NIH.

At one point, Wright pointed to the library's compact book collection and reminded the visitors that what you see isn't always what you get. With advanced computing ability and ever-expanding online resources throughout NIH, including more than 9000 scientific and medical e-books and access to all the major journals, he said, "Online we probably rank right up there with major medical center libraries" — despite the deceptively small physical facility.

NIEHS Biologist and Mebane resident Scott Gabel, left, talked with Wright about development in Orange and Alamance counties. Wright, a Cedar Grove resident, serves on the Orange County Planning Board as an advocate for responsible development. (Photo courtesy of Steve McCaw)

"They [newcomers at NIEHS and visitors] often just don't understand the specialized library," he continued, and its high level of individualized service and research support. A group of NIEHS scientists attending the reception, however, certainly did appreciate the library's contributions to science at NIEHS. Principal Investigator Ken Korach, Ph.D., spoke for many of them when he recalled "all the searches I'd never have gotten done without you."

Like Wright's patrons, his colleagues were sorry to see him go. "We will miss Larry terribly for his scientific expertise and droll humor," observed Library Director Dav Robertson, "but I'm making it a point to recruit a librarian with a strong science background and, hopefully, an equally keen sense of humor."

Wright retired in the same style he worked for the last 20 years — reminding his well-wishers of the NIEHS Library's 15-minute rule and dedication to service. "If you can't find what you need in 15 minutes on your own," he said, "you need to call one of us."

Following his retirement reception and a farewell luncheon with the rest of the library staff over the holidays, Wright set his sights on visits planned for this year to Italy and St. Bart's, as well as to museums and theatre in New York City.

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NIEHS Celebrates Legacy of M. L. King Jr.

By Eddy Ball

Oprah-bound motivational speaker Tawana Williams returned to NIEHS on Jan. 7 as part of the Institute's annual celebration of the achievements of Martin Luther King, Jr. Highlighting the theme of "Remember! Celebrate! Act! A Day On, Not a Day Off!" Williams' talk on "Focus on What You Want" linked King's collective dream to the aspirations of individuals to become all that they have the potential to be and use their talents to help others.

Co-sponsored by the NIEHS Diversity Council and the Research Triangle Park Chapter of Blacks In Government, the event opened with remarks from host Wanda Holliday on the significance of M. L. King Jr. Day for people of every race and ethnicity and closed with Williams' heart-felt expression of gratitude for the great leader's legacy. In between, Williams explored the ways that people can strive to achieve an inner freedom to reflect the external, collective freedom that King struggled for and died to realize.

With three books and several television appearances to her credit, Williams, above, looks forward to the biggest television appearance of her career later this year — an interview on The Oprah Winfrey Show. She is also working on a children's book with her daughter. (Photo courtesy of Steve McCaw)

Pursuing collective and individual dreams

While King's "I have a dream" speech focused on the aspirations of a people dispossessed because of race, Williams discussed the dreams of individuals — and the ways people can tap their inner power and overcome negativity, both their own and others'.

"I'm excited about the dream of Dr. King and his legacy," she began, "[And] I want you to think about your dream." Apropos of the day's theme, she also put the audience on the spot by asking, "Are you willing to open up your heart and your life to help somebody else?"

On her feet, animated, "in your face," and making eye contact with her listeners during an engaging monologue, Williams took full advantage of the rousing iambic pentameter and call-and-response rhythms of the traditional gospel church and the King James Translation to move her audience. They, in turn, responded with affirmations, laughter, and, at times, tears of epiphany and joy. Williams spoke candidly about hitting bottom several times — a victim of nay-saying, rape, and a ten-year crack cocaine addiction — and how she sprang back to achieve self-actualization and success.

NIEHS Administrative Officer Kim Peterson, center, and friends enjoyed Williams' upbeat humor. Seated beside her are colleagues Sharon Evans, left, and Gezell Jones. (Photo courtesy of Steve McCaw)

Born without arms, Williams has been defying negativism all her life. "Every time someone told me I couldn't do something," she told the audience, "the next time they saw me I was doing it."

Williams' message is deceptively simple — but, as she emphasized several times, one that too many people don't yet understand at the personal "gut" level. Williams' husband, Toby, the man she described as her "gentle giant," led the responses to her narrative, punctuating his wife's talk many times with "That's right!" as she told attendees, "There's some stuff in you [that] you didn't know you could do."

"It doesn't matter how many times you fall," Williams urged her audience, "you get up again and again and again."

During the question and answer segment of the event, NIEHS Human Resources Specialist Angela Davis, who was visibly moved by the presentation, echoed the sentiments of many in the audience. "I just want to thank you for what you've done for me today." Biologist Negin Martin, Ph.D., noted afterwards, "I wish my daughter and my friends could also hear her speak."

Program Analyst Trish Castranio was of one several audience members Williams addressed directly in the course of her monologue — one of the speaker's strategies for keeping people engaged. (Photo courtesy of Steve McCaw)

Toby Williams smiled as his wife told the story of how her "gentle giant" helped her rebound from a bout with crack cocaine addiction and encouraged her to try drawing. (Photo courtesy of Steve McCaw)

Diversity Council member Eli Ney, left, and host Wanda Holliday were obviously impressed by the speaker, as Williams showed off the drawings she completed using her feet and toes to hold and guide her pencil. (Photo courtesy of Steve McCaw)

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NIEHS to Implement New IT Governance Committee

By Eddy Ball

Although most employees aren't aware of all that the NIEHS IT (Information Technology) Governance Committee (ITGC) does, staff will soon begin to reap the benefits of its efforts, according to NIEHS Chief Information Officer Heather Nicholas and Computer Specialist Robin Jones.

Over the next fiscal year, promised IT projects will pass through a transparent unified evaluation and approval process designed to eliminate any duplication of services, satisfy legal and infrastructure requirements, and, where possible, integrate resources across offices, labs, and divisions to better support the Institute's pursuit of cutting-edge scientific excellence.

"This is a new process for the entire Institute," Nicholas explained. "IT project management is a key part of governance, [and] it's a huge undertaking." By developing a systematic approach to IT project management, however, Nicholas and Jones expect to boost services Institute-wide while getting the greatest payback for IT dollars spent.

With this new process, Nicholas added, "We're getting all the requirements [for new IT projects] up front to be able to meet the customer's needs in a better fashion, while still keeping the big picture in sight.… My goal is to make sure that the Governance Committee is able to see what's coming up for the next year."

The inter-divisional ITGC (see text box) and Technical Review Committee will be looking at new projects to determine how they fit into the totality of NIEHS IT needs and resources. As well as saving money, Nicholas said, coordinated IT project management will further reduce backlog to get new projects up and running on schedule with fewer bugs.

During IT project review, committee members will perform a rigorous cost-benefit analysis on proposed projects and identify the approximately 20 percent of new requests that can be implemented with commercial off-the-shelf (COTS) products and support. Each project will also have a timeline for implementation, list of project benefits, and clearly defined steps toward implementation.

Jones, left, and Nicholas are outlining ways to manage IT projects in an effective and transparent fashion as NIEHS takes advantage of advances in information technology to support its science. (Photo courtesy of Steve McCaw)

Makeup and Role of the ITGC

Members of the committee represent each division of the NIEHS/NTP. They are responsible for integrating the efforts of their respective communities, helping to identify their divisions' IT needs, communicating the total IT effort to their constituencies, and contributing to the overall transparency of the process. The ITGC also works hand-in-hand with the Technical Review Committee.

- Office of the Director — Acting Deputy Director Steve Kleeberger, Ph.D.
- Division of Intramural Research — Acting Scientific Director John Pritchard, Ph.D.
- Office of Management — Associate Director for Management Marc Hollander
- Division of Extramural Research and Training — Workers Education and Training Program Director Chip Hughes
- National Toxicology Program — Acting Chief of the Programs Operation Branch Cynthia Smith, Ph.D.

The ITGC will also prioritize enterprise IT projects according to criteria related to the Institute as an integrated whole:

- Mandated by regulatory agency
- Supports the NIEHS mission
- Makes a significant impact on science or administration
- Relates to an issue critical to health and safety
- Promises a positive return on investments
- Achieves a superior technical score

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