Environmental Factor
Your Online Source for NIEHS News

November 2007

NIEHS Spotlight

Science Notebook

NIEHS Spotlight

NIEHS Chemist Honored for Free Radical Research

By Eddy Ball

NIEHS chemist Ronald Mason, Ph.D., has received the 2007 Senior Investigator Lifetime Achievement Award from the Society for Free Radical Biology and Medicine (SFRBM). As part of this honor, Mason will present a featured lecture at the 14th Annual SFRBM Meeting at the Renaissance Hotel in Washington, D.C. on November 14. In addition, Mason will receive a $2,500 cash award and an invitation to publish a review article in the Society's journal, *Free Radical Biology and Medicine*.

Mason reported on his immuno-spin trapping methodology in the August 1, 2006 issue of Free Radical Biology and Medicine. In an accompanying commentary, SFRBM President-Elect Rafael Radi, M.D., Ph.D., praised Mason's innovation as "a potent, sensitive, and accessible method to detect low levels (e.g., greater than nanomolar) of protein-derived radicals." (Photo courtesy of Steve McCaw)

The award is an acknowledgement of Mason's major contributions to the detection and study of free radicals derived from or dependent on the metabolism of toxic chemicals, drugs and biomolecules. In the course of his 29 years with NIEHS, Mason has built upon his original training as a physical chemist in electron spin resonance (ESR) spectroscopy, which is the only general, but yet selective, method for the detection of free radicals.

Mason has made several ground-breaking discoveries related to the role of nitroreductase in drug toxicity and the free radical post-translational modification of proteins. His group has been very successful and productive using experimental rodent models in *in vivo* detection of the free radical mechanisms of diseases, such as endotoxin-induced acute respiratory distress syndrome, alcohol-induced liver damage and diabetes mellitus.

Currently a senior investigator and head of the NIEHS Free Radical Metabolite Section in the Laboratory of Pharmacology and Chemistry, Mason invented a novel immuno-spin free radical assay in 2002 that, according to SFRBM, "democratizes rigorous free radical detection." The new methodology offers researchers a cost-effective, validated assay that eliminates the need for highly expensive ESR equipment and the quantum mechanical expertise needed to operate it. The new technique produces orders-of-magnitude higher sensitivity and requires one-thousandth of the sample size needed for ESR — while also giving researchers the ability to analyze multiple samples simultaneously.

The author of more than 450 studies, Mason's previous honors include the prestigious International ESR Society Silver Medal and the Southern Chemist Award and Gold Medal given by the Southeast Region of the American Chemical Society. He is an accomplished instructor and mentor for junior scientists in training at NIEHS. In 2006, he received the Institute's Scientist of the Year Award.

At the SFRBM awards event, Mason will be joined by Robert A. Floyd, Ph.D., head of the Free Radical Biology and Aging Research Program at the Oklahoma Medical Research Foundation, who will be honored with the Society's Discovery Award.

Return to Table of Contents

Town Meeting Showcases IRB Process

By Eddy Ball

Scientists and other interested members of the NIEHS research community attended a Town Meeting in Rodbell Auditorium on October 1 to learn more about how to facilitate Institutional Review Board (IRB) approval of their research involving human subjects. Billed as "A Conversation between the Institutional Review Board and Clinical Investigators and Staff," the meeting featured presentations by key players in the IRB process, including an overview of efforts to fully automate the process.

With ample time reserved for questions and concerns, the meeting provided a forum for the growing number of NIEHS researchers required to seek approval for their studies. Among the speakers was Joan Packenham, Ph.D., program director in the Office of the Scientific Director and key person for development of the electronic management system, who traced the IRB process step by step for the audience.

In his opening remarks, Acting Director Sam Wilson, M.D., noted that the meeting was one of the Institute's responses to a "friendly audit" of the IRB in 2006, which recommended increased communication between the IRB and the NIEHS research community. He also underscored the importance of the IRB and the Board's continuing efforts to make the process more efficient.

Acting Scientific Director Perry Blackshear, M.D., D.Phil., presented a short history of measures to protect human subjects of research following the introduction of congressionally mandated regulations in 1974. The regulations initially were of limited concern to researchers at NIEHS, which had only five "active protocols," studies using humans and subject to approval, during the 1980s. At the current time, however, there are 49 active protocols, with even more anticipated as NIEHS begins research at its new Clinical Research Unit in 2008.

According to the meeting's keynote speaker, Marian Johnson-Thompson, Ph.D., chair of the NIEHS Institutional Review Board, the purpose of the IRB is "to protect the rights and safeguard the

"We hope that what we present today," Johnson-Thompson observed, "will convince you that we are really working for you." She also encouraged investigators to suggest ways to improve further the approval process. (Photo courtesy of Steve McCaw)

With his extensive experience in clinical research, Zeldin understands how time-consuming the preliminary and IRB approval processes can be. "It can take weeks to months to get the initial buy-in for a study," he said. (Photo courtesy of Steve McCaw)

Packenham discussed the Stakeholder Committee's "simplified" flow chart, which she distributed in the form of an eight-page handout. (Photo courtesy of Steve McCaw)

welfare of human subjects." Anyone working with human subjects and identifiable human specimens must seek IRB approval for a study before it can proceed — or obtain a formal waiver from the NIH Office of Human Subjects Research.

Johnson-Thompson outlined other measures NIEHS has taken in response to the 2006 audit, including the first-ever day-long IRB retreat and increased training for principal investigators. The IRB is developing its new Electronic Management System. In addition, Johnson-Thompson and Packenham have visited other NIH institutes and centers in search of ways to streamline the IRB process at NIEHS.

"We've also entered into discussions with intramural researchers about how the scientific review process could be enhanced," she added. "We are working now to resolve issues on a new component in the process, the conflict of interest element." Because consent form issues have been the leading reason for delays, "we want to develop a consent-form template… to prompt you to answer specific questions."

Senior Investigator Darryl Zeldin, M.D., addressed the overarching concern of researchers in his presentation, "Investigator Perspective: Why Is It Taking So Long?" Zeldin opened by noting "that the IRB approval process, while a significant component…, is only one of many processes and approvals an investigator needs to go through in order to be successful."

At any point in the process, an investigator may be required to revise the protocol and the many documents that are part of the study manual. In some cases, a study may also need approval by one or more external IRBs and, if contractors are involved, exemption from the Office of Management and Budget Review Board, in itself a nine- to twelve-month long process.

The meeting's final presenter was Community Member Betty Blackmon, who discussed her role as a non-affiliated lay member of the IRB. Blackmon acts as a non-scientific gatekeeper and scrutinizes the wording used in protocols, consent forms, surveys and other documents for subjects. "I want to be sure… [the written material] fully explains the study, risks and other information that they may need to determine whether or not they want to be a volunteer."

A former high school teacher, Blackmon looks for language that can be understood by someone with a seventh-grade reading level by red-flagging acronyms, technical jargon and culturally insensitive phrasing. (Photo by Steve McCaw)

As a bioethicist, David Resnik, J.D., Ph.D., is an active member of the IRB Committee. (Photo courtesy of Steve McCaw)

Protocol Specialist Darlene Switalski works with IRB Administrator Jane Lambert in support of investigators negotiating the IRB process. (Photo courtesy of Steve McCaw)

Return to Table of Contents

NIEHS Leads Global Environmental Health Forum in Bethesda

By Eddy Ball

In the most recent development in its Global Environmental Health (GEH) program, NIEHS sponsored a Forum, titled "How Partnerships Overcome Barriers to Improve Global Environmental Health," on September 28 at the Cloisters on the NIH Bethesda Campus. The gathering was designed to foster informal collaborative networks among U.S. and foreign public and private sector organizations with interests in GEH.

At the September 17 -18 meeting of the NIEHS National Advisory Environmental Health Sciences Council, Martin outlined the agenda of the upcoming GEH Forum. (Photo courtesy of Steve McCaw)

According to organizers, the day-long meeting gave individuals who normally have little occasion to interact with one another a rare opportunity to explore shared interests and potential partnerships that could offer mutual benefits and enhanced outcomes as a result of shared resources and expertise.

The meeting was co-chaired by William Martin, M.D., NIEHS associate director of Translational Research, and Jacob Moss, senior advisor in the U.S. Environmental Protection Agency (EPA) Office of Air and Radiation. The goal of the meeting was to identify cost-effective, sustainable partnership strategies with other government agencies, foundations, non-government organizations (NGOs), foreign governments, community groups and private industry to apply environmental health science in the developing world.

Participants were affiliated with a broad range of institutions, organizations and businesses. Private sector for-profit participants included Coca Cola, Enzen Global and Bosch-Siemens, makers of clean burning biomass cook stoves with the potential for reducing significantly the indoor air pollution that contributes to the deaths of 1.6 million individuals each year.

They were joined by funding sources, such as the Shell Foundation and the Global Environment and Technology Foundation, and NGOs. The latter ranged from the well-known World Health Organization to the grass-roots KIWAKKUKI, the Kilimanjaro (Tanzania) Women against AIDS, and the non-profit Population Services International, which harnesses the vitality of private sector marketing to address the health problems of low-income and vulnerable populations in more than 60 developing countries.

Dan Carucci of FNIH spoke to participants gathered at the Cloisters, a former convent of the Sisters of Visitation. (Photo courtesy of John Maruca)

In addition to Martin, NIEHS Acting Deputy Director Bill Suk, Ph.D., and Gwen Collman, Ph.D., chief of the Susceptibility and Population Health Branch in the Division of Extramural Research and Training, spoke at the meeting. NIEHS grantees making presentations on "Environmental Disease in the Developing World"

included Kirk Smith, Ph.D., Joseph Graziano, Ph.D., and Gerald Wogan, Ph.D. Grantee and former NIEHS National Advisory Environmental Health Sciences Council member Peter Spencer, Ph.D., was also in attendance.

The event brought together several federal agencies, including the EPA, Centers for Disease Control, U. S. Group on Earth Observations, the U.S. Agency for International Development and U.S. Department of State. Dan Carucci, M.D., Ph.D., director of the Foundation for the National Institutes of Health (FNIH) Grand Challenges in Global Health Initiative, spoke on public-private partnerships, and participants attended from the John E. Fogarty International Center, NIH Office of the Director, National Center for Minority Health and Health Disparities, National Heart, Lung and Blood Institute (NHLBI), National Institute of Allergy and Infectious Diseases, and National Institute of Child Health and Human Development.

Martin is currently working on a summary white paper on the forum and organizing reams of working notes from discussion groups. He envisions several possible options, but has no firm plans at this time, for future directions within the GEH program. There are massive challenges, he explained, but, from the NIEHS perspective, the key to addressing issues of environmental health in the developing world lies in bridge building and facilitating cooperative efforts.

Stressing the importance of such partnerships, Martin referred to an epigram by colleague Jacob Moss that he plans to include in the meeting summary: "The world is intuitively weaving itself into collaborative networks; those that do it better, prosper."

Shown here recording comments is Adam Wanner, M.D., a specialist in pediatrics and pulmonary disease at the University of Miami. According to Martin, some of the most valuable interchanges took place during the discussion sessions. (Photo courtesy of John Maruca)

Jim Kiley, Ph.D., standing, director of the NHLBI Division of Lung Diseases, was one of many attendees who took advantage of the forum's open discussion format. (Photo courtesy of John Maruca)

Return to Table of Contents

Epidemiology Branch Hosts *Sister Study* Advisory Meeting

By Eddy Ball

More than 43,000 women have joined *The Sister Study* so far. That was the good news highlighted by investigators and their colleagues in the NIEHS Epidemiology Branch during a September 27 meeting of the study's Scientific Advisory Board held in Rodbell Auditorium. The study has a goal of recruiting 50,000 sisters into its cohort by April 30, 2008.

The Sister Study is a unique long-term study of women aged 35 to 74 whose sisters had breast cancer. With the enormous data that will be available with a large and diverse cohort, the study is an unprecedented effort to understand the relative importance and interplay of genetic and environmental factors in the disease.

The full-day advisory board meeting surveyed progress in the study and examined future directions in data and sample collections, as well as ways to enhance study instruments and recruitment.

Even though enrollment has reached 86% of the initial goal, investigators said they are interested in developing contingency plans in case recruitment slows or the pool of volunteers does not adequately represent a diverse population.

One possible strategy is to continue recruitment efforts beyond the 50,000 goal and leave open the option of extending enrollment of under-represented groups of women — for example, those over 65 or with less than a college education, racial and ethnic minorities and those from specific geographical regions. An alternative is to "filter" enrollment as it approaches the 50,000 subject goal to achieve the desired proportion of priority women. During the meeting, participants heard progress reports by study staff and Epidemiology Branch Chief and Principal Investigator Dale Sandler, Ph.D. Attendees also learned about "Recent Findings in Whole Genome Association Studies" from National Cancer Institute Investigator and Scientific Advisory Board Member Montserrat Garcia-Closas, M.D., Dr.P.H.

Among the many challenges for the Scientific Advisory Board was coming up with suggestions for streamlining the next biennial follow-up. (Photo courtesy of Steve McCaw)

Sister Study Steering Committee Member Stephanie London, M.D., pondered a board member's remark as fellow Senior Investigator and Committee Member Jack Taylor, M.D., Ph.D., looked over study materials. (Photo courtesy of Steve McCaw)

In between speakers, Staff Scientist Jane Hoppin, ScD., made a point to board member Kent Thomas of EPA. (Photo courtesy of Steve McCaw)

NIEHS Biostatistics Branch Chief and Principal Investigator Clarice Weinberg, Ph.D., reported on the "Two-Sister Study." This parallel study, which is focusing on a cohort of 2,000 women, is an investigation of the genetic and environmental causes of young-onset breast cancer.

The meeting concluded with a session on study follow-up planning. Sandler discussed the current biennial follow-up questionnaire and the possible addition of sample collections, such as saliva or buccal cells, to the blood, urine, toenail clippings and dust samples currently collected at baseline. Participants also addressed long-range planning issues for nested studies of genes and gene-environment interactions and specific outcomes, as well as follow-up of participants who develop breast cancer.

The Sister Study Scientific Advisory Board is composed of research scientists and clinicians from NIH institutes, the United States Environmental Protection Agency, universities and organizations from across the country and also includes two community liaisons and representatives from the American Cancer Society, the National Center on Minority Health and Health Disparities, Susan B. Komen for the Cure, the International Cancer Council, Y-Me Breast National Cancer Organization and Sisters Network, Inc.

Return to Table of Contents

Sister Study Project Principal Investigator Dale Sandler, left, listened to comments on future directions from Patricia Hartge, ScD., deputy director of the National Cancer Institute's Epidemiology and Biostatistics Program. (Photo courtesy of Steve McCaw)

During a mid-day break, the board gathered for a group photo on the patio outside Rodbell Auditorium. NIEHS scientists shown in the front row include London, second from left, Sandler, fourth from left in black and white, and Weinberg, seated at the far right. (Photo courtesy of Steve McCaw)

Hrynkow Appointed as NIEHS Associate Director

By Robin Mackar

Sharon Hrynkow, Ph.D., joined the NIEHS as a new associate director on October 15, 2007. She will work with the NIEHS senior leadership team on a range of program and management activities, including trans-NIH initiatives, partnership building with federal agencies and others, and extramural community outreach. She is assigned to the NIEHS office in Bethesda, Md. and will be a visible presence representing the mission of the NIEHS/NTP to various communities in the DC metropolitan area.

NIEHS Associate Director Sharon Hrynkow (Photo courtesy of Sharon Hrynkow)

"I am very pleased to welcome Dr. Hrynkow to NIEHS," said Samuel Wilson, M.D., NIEHS acting director, in his announcement of the appointment. "I have known her professionally for several years and believe she will be an extremely effective advocate for NIEHS."

Hrynkow has held leadership positions at NIH for 10 years. For much of that time, she worked at the Fogarty International Center (FIC), first as the FIC Deputy Director and, from 2004 to 2006, as acting director. During the past year, she took a sabbatical from her permanent position in the NIH Office of the Director to serve as senior advisor for the United Nations Foundation.

Hrynkow is well known at NIH for her ability to build new partnerships and develop innovative research and training programs. She worked with virtually every IC during her tenure at FIC and helped establish and maintain particularly strong ties to NIEHS.

"I am delighted and honored to have the opportunity to help NIEHS advance its critical mission," Hrynkow commented. "In many ways, the role at NIEHS builds on my previous experiences, [and] I look forward to the action agenda."

A career civil servant and member of the Senior Executive Service with advanced training in neuroscience, Hrynkow brings a wealth of leadership experience in tackling global health issues to her new position. Prior to joining NIH, she was a science officer at the US Department of State, where she played a key role in helping the diplomatic corps address the emerging issue of HIV/AIDS.

Hrynkow serves on a number of professional and non-governmental committees and Boards, including the Institute of Medicine Roundtable on Environmental Health Sciences, Research and Medicine, and the AAAS Committee on Science, Engineering and Public Policy. She has received numerous awards and honors in recognition of her achievements, including the Presidential Meritorious Executive Rank Award and the King of Norway's Order of Merit.

Return to Table of Contents

Success in Health Disparities Research

By Robin Arnette

In one of several activities held to celebrate Hispanic Heritage Month, NIEHS welcomed Gloria Coronado, Ph.D. who shared a few of her success stories during a seminar, titled "Health Disparities Research in Agricultural Communities in Washington State," held in Rodbell Auditorium on October 3. Coronado is an assistant professor in the Department of Epidemiology at the University of Washington and an Assistant Member in the Cancer Prevention Program at the Fred Hutchinson Cancer Research Center (FHCRC) in Seattle, Washington.

Coronado's work bridges the gulf between the health care system and migrant farm workers, a group that is all but invisible to most American consumers. (Photo courtesy of Steve McCaw)

Rosemarie Ramos, Ph.D., a postdoctoral fellow in the Laboratory of Molecular Carcinogenesis and a member of the NIEHS Diversity Council, hosted the seminar. Ramos was pleased that Coronado was able to make the cross-country trip and said, "Dr. Coronado's research helps to fill the void of what we still do not understand about health disparities within the U.S. migrant worker population."

Under the mentorship of Beti Thompson, Ph.D., at FHCRC, Coronado worked on a cancer prevention program that focused on understanding different cancer screening behaviors and lifestyle practices in the Yakima Valley in southeastern Washington State. She and colleagues hired and trained bilingual/bicultural individuals to conduct in-person surveys in 20 communities in 1998. They selected 1800 households for interviews and asked whether adults had received a colonoscopy, mammogram or Pap test.

Ramos was host for both of the scientific presentations held as part of Hispanic Heritage Month. (Photo courtesy of Steve McCaw)

The results determined that a majority of the respondents had not received any of these tests, even if they had the resources to pay for them. Respondents listed a variety of reasons for not participating in preventive care, but one of the prevailing thoughts was that Hispanics don't want to know if they have cancer. According to Coronado, one of the respondents said, "The doctor is often asked to talk about the diagnosis of the disease [only] with the patient's relatives."

To combat these beliefs, Coronado's team decided to take a community approach. By forming an advisory board that included individuals from 18 different organizations, the team was able to receive funding for a Special Populations Network. The Network funded community activities, such as the Student Cervical Health Program, Smart Nutrition Choices and the Prostate Cancer Radio Outreach Program.

In the next portion of the talk, Coronado discussed the For Healthy Kids! project. Its goal was to reduce pesticide exposure, specifically in children, by developing a culturally appropriate intervention to break the take-home pesticide pathway. The team formed a community advisory board, identified about 600 families in the area, and collected urine and dust samples from families in 24 labor camp communities in the spring of 1999.

The team looked at non-pome fruit (grapes, cherries and asparagus) workers and pome fruit (apples and pears) workers and found that the most common urinary metabolite was DMTP (0,0-dimethyl-s-(2-methoxy-1,3,4-thiadiazol-5(4H)-onyl-(4)-m ethyl)- dithiophosphate). DMTP is a breakdown product of azinphos-methyl, the most used organophosphate in Yakima Valley.

The most interesting finding was that pome fruit workers had a higher percentage of detection and higher concentrations of DMTP than non-pome fruit workers. Also, pome fruit workers who worked with both apples and pears had slightly higher exposure levels than those who worked with either apples or pears. The data for the children of pome fruit workers was similar to the adult values, which suggested the children were being exposed to pesticides via their parents. The results provided a stimulus for farm workers to employ good safety practices such as removing work boots before entering the home.

Coronado and her colleagues received recognition in a local Washington newspaper and as a result, donors contributed an additional $120,000 to expand the research. The researchers used the money to collect blood, saliva and buccal cell samples, and they added cholinesterase monitoring. They also provided the families with their study results and additional education materials in regard to pesticides.

Coronado said that one of the most fulfilling aspects of the unexpected financial windfall was the establishment of a summer interns program. “[This money] allows us to train underrepresented [minority] students in cancer research and pesticide research, and it really has an impact on encouraging them to go to college,” she said. “It gives me joy to participate in their training.”

Return to Table of Contents

Physician-Scientist Touts Bottom-up Community Education

By Eddy Ball

Working to improve environmental health for residents along the Texas-Mexico border and in the metropolitan area of Louisville, Kentucky, Irma Ramos, M.D., has learned firsthand the difference that bottom-up community involvement can make in the success or failure of outreach and health education efforts. On October 10, as part of Hispanic Heritage Month, the University of Louisville School of Public Health professor shared her insights with an audience in Rodbell Auditorium. Her lecture, titled “Improving Hispanic Health: A Culturally Sensitive Approach,” was hosted by Postdoctoral Fellow Rose Ramos, Ph.D., and sponsored by the NIEHS Hispanic Heritage Month Committee.

A veteran NIEHS grantee, Ramos addressed common themes in environmental justice and community-based participatory research — how to encourage socially or physically isolated communities to take ownership of environmental health projects. (Photo courtesy of Steve McCaw)

Irma Ramos said approximately 1,800 "colonias," or neighborhoods, exist along 1,248-miles of border between the United States and Mexico border with an estimated population of more than 500,000 people, 98 percent of them Hispanic. Of these, 65 percent — and about 85 percent of residents under 18— were born in the United States. Ramos said these residents live in poverty and unsanitary conditions with very little community support.

Ramos' work focused on the communities of Progresso, San Carlos, Las Milpas and Cameron Park in South Texas. As she explained, the objective of the project was "to translate major research findings in the environmental health sciences into practical concepts that can be easily adopted by rural communities in Texas."

As part of the project, Ramos and her team accessed an important resource within the colonias — the network of "promotoras" or lay educators and community health workers who are widely known and trusted members of the community. In South Texas colonias, promotoras are certified members of a professional association and paid just above minimum wage for their services as part-time community liaisons.

"This bottom-up model of education," Ramos observed, "ensures that the community will support the program and that the program will continue in the community even after the research project is finished."

Outcomes analysis of data from Texas is still ongoing, but Ramos said that results so far are encouraging. Comparing pre- and post-intervention results, she found increases in environmental health literacy among promotoras and subjects, and data collected at the beginning of the project pinpointed health needs that should be addressed in future efforts and documented suspected environmental health risks. The study is being published in an upcoming issue of the *Journal of Immigrant and Minority Health*.

Biologist Lysandra Castro listened as Program Analyst Liam O'Fallon asked Ramos about whether her project has influenced policy change along the Texas-Mexico border. (Photo courtesy of Steve McCaw)

After moving to Kentucky, Ramos encountered several region-specific challenges to using the same model in the Louisville metropolitan area of Jefferson and Shelby counties. There, the Hispanic population has grown rapidly, increasing 173 percent between 1990 and 2000. The population is far less cohesive than the population in South Texas, as well as more diverse, representing 20 Spanish-speaking countries. The region has a weaker social support network, and little is known about the population's needs, concerns and environmental risks.

Because of the fragmentation and transience of the Hispanic population in Kentucky, the project is being forced to build a promotoras infrastructure virtually from scratch. Along with language barriers related to dialects and indigenous languages, the population includes more undocumented individuals than the Texas population, making the promotoras approach even more critical to success of the project.

Ramos is a pediatrician and public health specialist with research interests in the fetal basis of environmental disease, cancer and occupational health. She served as the director of Community Outreach and Education in the National Institute of Environmental Health Sciences Center for Environmental and Rural Health at Texas A & M University. In October 2003, Ramos accepted her current academic appointment and later assumed the position of director of Community Outreach and Education with the Environmental Health Sciences Core Center at the University of Louisville.

Spreading the Word in Hispanic Communities

On October 11, 2007, the Centers for Disease Control and Prevention (CDC) Spanish-language Web site, *CDC en Español*, was re-launched with a new look and new features that will make it more usable and functional. The updated Web site is another important step in CDC's longstanding efforts to provide accurate, up-to-date information in Spanish on health issues of special interest to Hispanic communities, including information on a wide range of health promotion and disease prevention topics like asthma, cancer, HIV/AIDS, immunizations, children's health, diabetes and occupational hazards. The *CDC en Español* Web site address is www.cdc.gov/spanish.

Among the new features on *CDC en Español*:

- Health and safety information is now grouped in broad, easy-to-browse topic areas.
- Additional new features provide better access to data and statistics, recent news, tools and resources, and new publications.
- A new Google-based search engine provides more relevant search results.
- An interactive features area at the top of the home page highlights a number of current issues, events and health topics of particular interest to Hispanic audiences with relevant photographs or videos. This feature enables *CDC en Español* to better display health recommendations, guidelines and upcoming events.
- A "Top 20" section allows visitors to quickly view a list of the most popular health topics, and access each directly from the home page.

Take a Virtual Tour of the new *CDC en Español* site at http://www.cdc.gov/spanish/especialesCDC/tour.html

Send an ecard to share the new *CDC en Español* with others – http://www2a.cdc.gov/ecards/spanish/

Subscribe to *CDC en Español* listserv – http://www.cdc.gov/spanish/suscribase.html

Link to *CDC en Español* – Organizations are encouraged to offer a text link or graphical link to the *CDC en Español* Web site to provide Web visitors with direct access to CDC's Spanish – language health information. http://www.cdc.gov/spanish/CDC/enlacese.html.

CDC en Español now receives over 6 million visitors a year and its weekly distribution list has grown to almost 6,000 members in over 40 countries around the world.

Return to Table of Contents

NIEHS Takes Home Big Check from Avon Walk

On October 22, NIEHS Health Scientist Administrator Les Reinlib, Ph.D., who directs the Breast Cancer and the Environment Research Centers Program, accepted a check for $530,000 from the Avon Foundation to support expanded breast cancer research. The money is part of proceeds from a record-breaking event involving more than 1,050 participants in the third annual Avon Walk for Breast Cancer in Charlotte on October 20 -21.

NIEHS received the largest grant made at the event. The Institute will use the grant for expansion of the Avon-NIEHS partnership for the Breast Cancer and the Environment Research Centers, funding community advocate involvement and the coordination of studies. The funds will help support investigations into the role of possible environmental and genetic factors and future risk of breast cancer.

At the Awards Ceremony, Reinlib, center, posed with Marc Hurlbert, scientific director for the Avon Foundation and Karen Borkowsky, program director of the Avon Walk for Breast Cancer. (Photo courtesy of Les Reinlib)

This year's volunteers raised $2.3 million to advance access to care and search for a cure for breast cancer by completing walks sponsored by donors. To participate in the Avon Walk Charlotte, each volunteer had to raise a minimum of $1,800 and complete a marathon, equaling 26.2 miles, or a marathon and a half, totaling 39.3 miles, over the weekend.

Funds raised by participants of the Avon Walks are awarded to local, regional and national breast cancer organizations to support five areas of the breast cancer cause, including awareness and education, screening and diagnosis, access to treatment, support services and scientific research, all with a focus on the medically underserved. Along with NIEHS, three other organizations in the Carolinas received proceeds from the walk:

- Duke University in Durham, N.C. — $250,000 to support expansion of Duke's outreach to the African-American Community in Raleigh, Greensboro and Charlotte, as well as patient navigation services
- Medical University of South Carolina (MUSC) in Charleston, S.C. — $250,000 to continue the Avon-MUSC Patient Navigation Program, which was established through Avon Foundation funding in 2005
- Presbyterian Hospital in Charlotte, N.C. —$150,000 to expand community outreach and patient navigation services to better reach underserved communities in Charlotte, Mecklenburg County and eleven surrounding counties.

Since 2003, the Avon Walk for Breast Cancer series raised more than $175 million. The 2007 Avon Walks has raised more than $45 million. Donations are still being accepted for the Avon Walk Charlotte, and registration is open for the upcoming 2008 Avon Walk series. The 2008 series kicks off in the event's newest city, Houston, on April 12-13 and once again will be held in Charlotte; Washington, DC; Boston; Chicago; Rocky Mountains; San Francisco; Los Angeles and New York.

Return to Table of Contents

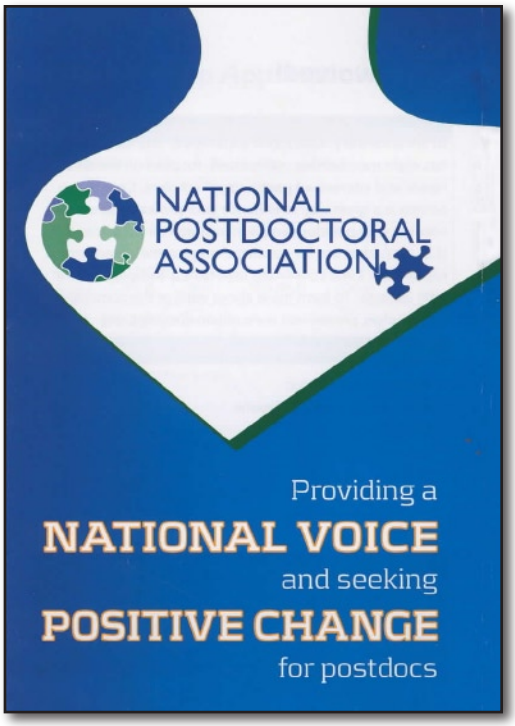
Trainees Welcome National Postdoctoral Association Director

By Eddy Ball

Some twenty NIEHS trainees took advantage of Executive Director Alyson Reed's visit to the Institute on September 27 to learn what the National Postdoctoral Association (NPA) can do for them and their careers. The reception and informal talk took place in the Executive Conference Room and was hosted by the NIEHS Trainees Assembly (NTA) and NIEHS Office of Fellows Career Development (OFCD).

Reed assumed her position as the NPA Executive Director in 2003 and has worked closely for several years with OFCD Acting Director Diane Klotz, Ph.D. Klotz has been a member of the NPA since 2004, a member of the NPA Policy Committee prior to becoming a Board of Directors member in 2006 and chair of the NPA Board of Directors for 2007.

During her tenure at NPA, Reed has taken the organization from a struggling, all-volunteer organization to a proactive force in postdoctoral training with a staff of full-time professionals (see text box). The NPA has a comprehensive agenda, Reed pointed out, for "essentially changing the climate for postdoctoral training in the United States."



NIEHS Summers of Discovery and Special Programs Coordinator Charle League also attended the meeting. As Klotz explained, there will be more collaboration between OFCD and Summers of Discovery programs in the future, improved long-term scheduling of training programs and greater structure for the curriculum and career development opportunities for fellows at every level.

"There will be a better integration of scientific training with career development," Klotz continued, "[to] actually bring you as fellows into a more formal mentoring of the Summers of Discovery participants, …[which could include] participating in the seminar series and gaining teaching experience you can include on a CV."

During an informal interchange between Reed and the trainees, questions and comments tended to focus on career issues, such as the importance of expressing trainee and principal investigator expectations. Reed emphasized the value of creating a structured Individual Development Plan at the beginning of the apprenticeship.

Placement patterns are changing, she noted, with fewer trainees moving on to traditional tenure-track positions. Several trainees at the reception expressed concerns about the return on their investment of time and money in graduate school and advanced scientific training.

After the meeting concluded, Reed talked with individual trainees about specific needs and concerns. (Photo by Eddy Ball)

Reed readily conceded that neither the national association nor individual institutions have access to sufficient data for analyzing employment trends, market-focused training needs, earning trajectories and the influence of different kinds of training on outcomes. She pledged to continue efforts to improve the situation. "We want an evidence-based policy arena," she observed, "instead of relying on anecdotes."

However, Reed also underscored the opportunities that trainees already have for gaining more control over their training. "Your principal investigators can't cover every base," she concluded. "The idea is to articulate what your interests are and map out a plan for how you are going to get the exposure to those environments where you might want to work."

Overview of the NPA

Advocacy – Both at the national level and at the level of individual institutions, the organization lobbies to establish standards and procedures to ensure that fellowships are in fact a temporary period of mentored apprenticeship, rather than an extended holding pattern with postdocs providing inexpensive, talented labor. In addition to issues of compensation, the NPA has called for policies to promote quality mentoring and measures to encourage both the fellows and their mentors to emphasize this component of the training experience. Since 2003, over 130 institutions have adopted at least some of the group's *Recommendations for Postdoctoral Policies and Practices*.

Resource Development — Data collection and analysis are important services provided by the NPA. There are enormous gaps in the information available to trainees and their institutions, including exactly how many fellows are in training, what their demographics and working conditions are, and how their careers unfold after they transition from training. This information is relevant to trainees both in their current positions and later when they become trainers and mentors themselves.

In addition to its newsletter and e-mail updates, the NPA helps trainees with a host of practical matters with such resources as the *International Postdoc Survival Guide* and Job Bank, and it provides models for institutions, including sample text in the publication on *Developing a Postdoctoral Fellows Handbook*.

Community Building — Before the NPA, there was no nucleus for the people and institutions involved in postdoctoral training. Currently, the organization has 150 sustaining institutional members, representing over 40,000 trainees, and thousands of individual, affiliate and friends-of-NPA members. This continually expanding network helps to keep postdocs and their employers informed and communicating, and it is a driving force in ongoing efforts by the NPA to maintain the momentum of positive change in the climate of postdoc training and to give trainees a greater sense of empowerment.

The NPA has compiled an impressive list of NPA Accomplishments 2003-2006.

Return to Table of Contents

Science Notebook

The Role of Calcium in Heart Failure

By Robin Arnette

As part of the 2007–2008 Distinguished Lecture Series, NIEHS researchers were treated to an engaging discourse on the role of calcium in heart failure by Andrew R. Marks, M.D., professor and chairman of the Department of Physiology and Cellular Biophysics at the Columbia University College of Physicians and Surgeons. His lecture, titled "Defective Calcium Regulation as a Cause of Heart Failure and Sudden Cardiac Death," took place on October 9 in Rodbell Auditorium. James Putney, Ph.D., head of the Calcium Regulation Group in the Laboratory of Signal Transduction, hosted the seminar.

Distinguished Lecture Andrew Marks (Photo courtesy of Steve McCaw)

Marks began by reminding the audience that heart failure is the leading cause of death in the U.S. and the developed world. The condition afflicts about 5 million patients in the U.S., with nearly half a million new diagnoses each year. Sudden cardiac death, a closely related disorder, claims about half a million American lives annually, with over 60% of all patients with some form of heart disease dying suddenly. Marks said that for decades physicians never understood why tissue biopsied from hearts that had undergone heart failure looked normal under the microscope.

Lecture host Jim Putney, an authority on calcium signaling. (Photo courtesy of Steve McCaw)

The answer, he proposed, has to do with defective calcium regulation during excitation-contraction coupling. Marks said excitation-contraction coupling occurs during each heart beat and every time a person moves a limb.

"When muscle membranes—both skeletal and cardiac—become depolarized or electrically activated, an electrical signal travels down the transverse tubule where it activates a voltage-dependent calcium channel in the transverse tubule," Marks explained. "Calcium then binds to the calcium release channel, made up of four monomers of ryanodine receptors (RyR), releasing a much larger store of calcium from the sarcoplasmic reticulum, which causes the contractile filaments to contract. Relaxation occurs when the calcium is pumped back into the sarcoplasmic reticulum."

Marks said it was critical that the RyR channels stay tightly closed during times that muscles are relaxed. If not, calcium can leak and the individual could have a defect in moving the limbs or allowing the heart to relax to refill for the next contraction.

In the late '80s in collaboration with protein chemist Paul Temps, Marks cloned the ryanodine receptor and also discovered a smaller protein, which subsequent experiments led him to call the calcium channel-stabilizing binding protein or calstabin. "We expressed ryanodine receptor in SF9 insect cells, one of only a few types of cell that don't express calstabin, isolated the ryanodine receptor channel and measured the channel's activity," Marks said. "In the absence of calstabin, the channel leaked calcium and never stayed in the open or closed state." In contrast, when Marks co-expressed calstabin with the ryanodine receptor, the calstabin fixed the "leakiness" because the ryanodine receptor demonstrated long and stable closed states.

Once Marks knew that calstabin stabilized the ryanodine receptor, he wanted to understand the mechanism of action. It turned out that the process was involved in the classic fight or flight stress response. Marks' group determined that cyclic-dependent protein kinase A (PKA) phosporylated one serine residue within the ryanodine receptor (Ser2808), but since four ryanodine receptors make up the ion channel, three or perhaps all four of the Ser2808s may be phosphorylated.

This hyperphosporylation state, which occurs in damaged hearts, depletes the calstabin, thereby destabilizing the channel and causing the calcium leak. "Over time this depletes the precious pool of calcium in the sarcoplasmic reticulum and instead of increasing contractility, you decrease cardiac output," Marks declared. "These events have been associated as molecular triggers of ventricular arrhythmias [alteration in heart rhythm]."

Return to Table of Contents

Marks' lecture drew a capacity crowd to the Rodbell Auditorium. (Photo courtesy of Steve McCaw)

Using Drug Therapy to Prevent Heart Failure

Beta-blockers, one of the most widely prescribed drugs in the world, fix the calcium leak in ryanodine receptors by preventing PKA activity, but the drugs also block all phosphorylation events in the body, some of which are necessary for proper function. Therefore, Marks and his team started with JTV-519—a compound synthesized by Japanese chemists during the development of diltiazem (Cardizem), the highly used calcium channel blocker—and synthesized over 440 chemical derivatives. These compounds fix the leak in RyR channels by preventing the depletion of the calstabin from the PKA-hyperphosphorylated ryanodine receptor by causing a conformational change of the receptor. Marks and his group named them rycals or calcium channel stabilizers and have since created a company at Columbia to mass produce oral versions of the derivatives. Clinical trials using rycals will begin in April 2008.

"These compounds are 100 percent specific to the ryanodine receptor and are water soluble," Marks stated. "A Japanese group, using another mammalian heart failure model, has confirmed that rycals improve cardiac function, fix the calcium leak and restore calstabin binding to the ryanodine receptor. We are very proud of our work because it may help millions of patients with heart disease."

Wilson Gives Keynote Talk at Genome Stability Meeting

By Eddy Ball

NIEHS Acting Director Sam Wilson, M.D., delivered the first of three keynote lectures at the October 13 "Determinants of Genome Stability in Human Disease" conference held in Chapel Hill at the William and Ida Friday Center for Continuing Education. The North Carolina regional conference and poster session was jointly sponsored by NIEHS, antibody supplier Abcam, Inc., the University of North Carolina (UNC) Lineberger Comprehensive Cancer Center, the Duke Comprehensive Cancer Center and North Carolina State University (NCSU).

At the beginning of his talk, Wilson reinforced the networking/ collaboration theme of the conference. "I'm looking forward to interacting with all of you." (Photo courtesy of Steve McCaw)

Wilson was joined at the podium by NIEHS Laboratory of Structural Biology Chief and DNA Replication Fidelity Group Head Tom Kunkel, Ph.D., NIEHS Postdoctoral Fellow Mercedes Arana, Ph.D., and three Triangle-area NIEHS grantees: Conference Coordinator Marila Cordeiro-Stone, Ph.D., of UNC, her colleague William Kaufmann, Ph.D., and Robert Smart, Ph.D., of NCSU. Other speakers included National Institute of Diabetes and Digestive and Kidney Diseases Peggy Hsieh, Ph.D., Lawrence A. Loeb, M.D., Ph.D., of the University of Washington, Seattle, and Duke's Thomas D. Petes, Ph.D., and Sue Jinks-Robertson, Ph.D.

NIEHS grantee Cordeiro-Stone, above, worked with Jinks-Robertson, Kunkel and Smart to organize the conference. (Photo courtesy of Steve McCaw)

Wilson's talk was titled "Structural and Mechanistic Insights into Genome Protection through Base Excision Repair (BER)." The talk grew out of ongoing crystal–structure studies with his DNA Repair and Nucleic Acid Enzymology Group on repair pathways, sequential steps and substrates involved in the BER process.

"A whole range of events in the cell can lead to DNA damage that is repaired by BER," Wilson began. "And we're learning more and more every day about the importance of oxidative stress in inflammation and other processes. This type of stress leads to DNA damage, and this damage, in part, is repaired by BER."

Throughout his talk, Wilson underscored the elaborate orchestration, the "fascinating system of complexity," that takes place in the course of DNA repair. Better understanding of these mechanisms can help scientists gain insights into an organism's failure to repair endogenous and environmentally induced damage to DNA, the effects of polymorphisms, such as ones affecting activity levels of the protein molecules XRCC1 and polymerase beta, and the ways these mechanisms relate to chemotherapy, such as the use of a DNA alkylating agent to combat tumor growth.

Wilson outlined the steps in the repair of DNA single-base lesions, including lesion removal, strand incision, gap filling, gap tailoring, flap removal and strand ligation. “There are many complexities and variations in each one of these steps,” he explained, “and there are many enzymatic redundancies. For example,… in the gap-filling step there are more than a dozen… enzymes [that] can, under appropriate conditions, conduct gap filling.”

Other speakers reported on mechanistic studies in yeast and specific mechanisms, such as mismatch repair and human replication fork protection complex. The talks progressed to the potential translational level with talks by Smart and Loeb on applications of genome stability research to human cancers.

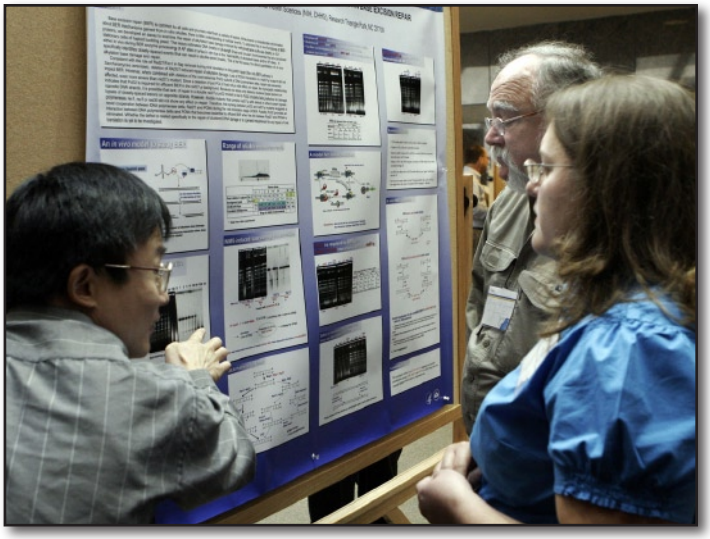
Kunkel, whose lab was well-represented at the poster session, spoke briefly on the aims and focus of the conference. “The idea here, the primary objective,” he observed, “is to exchange unpublished and published information on the DNA transactions that determine genome stability, the mechanisms by which these transactions operate and how the failure of those DNA transactions are associated with human health consequences.”

Cordeiro-Stone’s remarks underscored the value of the meeting as a forum for regional investigators and as a networking/collaboration venue for postdocs and junior investigators. The meeting included two 90-minute poster sessions, showcasing a total of 41 abstracts and posters, a networking lunch and an evening reception. The format offered postdocs and junior investigators several opportunities for interacting with the speakers and with each other.

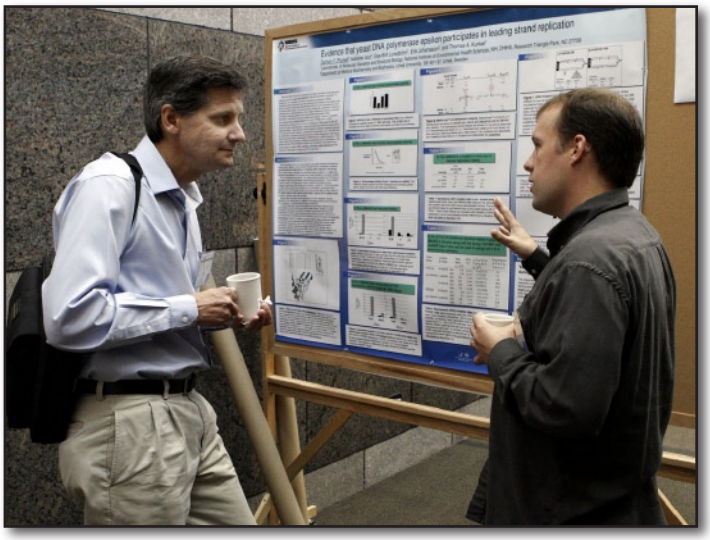
Along with its impressive schedule of speakers, the conference was also notable for the time and attention it gave to postdocs and junior researchers. Shown here, left to right, are Laboratory of Molecular Genetics (LMG) Chief Jan Drake, LMG Visiting Fellow Miguel Garcia-Diaz, Ph.D., and Kunkel. (Photo courtesy of Steve McCaw)

Kunkel, right, closed his presentation file as Arana began her introduction of Wilson. Arana also staffed her poster, which reported on structure-function analysis of DNA binding. (Photo courtesy of Steve McCaw)

Former postdoctoral fellow Kirill Lobachev, Ph.D., right, now at the Georgia Institute of Technology, talked with his mentor, LMG Supervisory Research Geneticist Mike Resnick,Ph.D. Lobachev's poster reported on his study of compromised replication fork progression. (Photo courtesy of Steve McCaw)



There is no mistaking the enthusiasm of Visiting Fellow Wenjian Ma, Ph.D., as he talks about his work in Resnick's lab. Ma's study examined a novel role for the yeast Pol32 subunit of DNA polymerase delta in BER. (Photo courtesy of Steve McCaw)



IRTA Fellow Zack Pursell, Ph.D., discussed ground-breaking work in the area of leading strand DNA replication performed in Kunkel's lab. (Photo courtesy of Steve McCaw)

NIEHS grantee and conference presenter William Kaufmann took advantage of the poster session break to enjoy a cup of coffee as he looked at displayers' abstracts. (Photo courtesy of Steve McCaw)

[Return to Table of Contents]

Toxicogenomics Report: New Tools to Assess Risks from Chemicals

By Robin Mackar

Determining how thousands of chemicals found in the environment may be interacting with the genes in the body to cause disease may become easier and more cost-effective, thanks to advances in the field of science known as toxicogenomics. A new report issued October 9 by the National Academies of Sciences (NAS) recognizes the importance of alternative high-throughput methodologies in predicting effects on human health and recommends the integration of toxicogenomics into regulatory decision making.

The NAS report, Applications of Toxicogenomic Technologies to Predictive Toxicology and Risk Assessment, was commissioned by NIEHS, a leader in the development of toxicogenomic technologies. Over the past decade, NIEHS has promoted the development of advanced technologies for identifying the biochemical pathways of toxicity as a viable alternative to animal studies, which are several times more expensive and time consuming.

Because of their speed, cost and capacity for processing large volumes of data, toxicogenomic technologies offer researchers a way to address the growing backlog of chemicals whose potential toxicity has yet to be assessed. The National Toxicology Program (NTP) has also endorsed development of alternative methodologies as one answer to concerns by the animal rights community over the use of animals in research.

Toxicogenomic technologies provide tools to understand more completely the mechanisms through which environmental agents initiate and advance disease processes. They can also provide important information to help identify individuals who are more susceptible than the general population to disease risks posed by certain environmental agents.

“Using toxicogenomic technologies will open the door for public health decision makers who need to decide in a timely and accurate manner what chemicals are safe and which ones are not,” said Christopher Portier, Ph.D., associate director, NIEHS and director, Office of Risk Assessment Research.

The report from the NAS National Research Council (NRC) states that the technological hurdles that could have limited the reproducibility of data from toxicogenomic technologies have been resolved and recommends ways for the field to move forward.

“NIH and others have invested in the development of these tools and have already tackled many of the tough technical questions. We are now ready to move to the next phase of technology development, refined standardization and validation, so these tools can be even more useful to regulatory agencies,” said Portier.

“The NIEHS and NTP have been steadily increasing the use of toxicogenomic and other technologies derived from the molecular biology revolution,” said Samuel H. Wilson, M.D., NIEHS acting director. The research and initiatives supported through the National Center for Toxicogenomics and the Toxicogenomics Research Consortium, for example, were at the forefront of these technologies and were instrumental in the development of many of the standards for quality and reproducibility that are used today.

The report, which was prepared by a panel of 16 scientists assembled by the NRC and chaired by Harvard University’s David Christiani, Ph.D., provides a broad overview of the potential benefits arising from toxicogenomic technologies, describes challenges regarding use of new technologies and provides 14 recommendations to achieve the potential benefits of these technologies.

Return to Table of Contents

Superfund Grantee Speaks on "The King of Poisons"

By Eddy Ball

NIEHS Superfund Basic Research Program grantee Vasken Aposhian, Ph.D., enlightened and entertained a standing-room-only audience in Rodbell Auditorium on October 17 with his talk on arsenic. Titled "The King of Poisons, the Poison of Kings and the Bane of Investigators," Aposhian's Superfund Distinguished Lecture focused on what he considers to be the three milestones in arsenic research since the 1980s, when Superfund support revived investigations into the biochemistry and health risks of the ubiquitous element.

Aposhian, whose lecture was hosted by Superfund Acting Director Claudia Thompson, Ph.D., is currently a professor in the Department of Molecular and Cellular Biology at the University of Arizona. In the course of a career spanning over fifty years, he has distinguished himself in the area of molecular mechanisms of toxic metals.

Because the problem is not just arsenic, but also the element's metabolites, Aposhian told the audience, "I don't know of another cancer system that is as complicated as the arsenic cancer system." (Photo courtesy of Steve McCaw)

"He is truly an internationally recognized expert in the area of metal intoxication," Thompson said of his numerous invited lectures and extensive travel overseas.

The Superfund Program, which is set to celebrate its 20th anniversary in December, was founded in 1987 — the same year that the National Science Foundation (NSF) turned down Aposhian's request for funding to study arsenic. According to Aposhian, an NSF reviewer commented, "It's a very exotic subject, but everyone knows that everything is known about arsenic. There's nothing else to be done."

Not long afterward, with Superfund support, Aposhian's group and others set out to prove the reviewer wrong. In the intervening 20 years, Aposhian observed, this research has helped millions of people worldwide better appreciate the health threat posed by arsenic in the water they drink, the food they eat and the air they breathe.

A favored means of murder called the "inheritance drug" in France, arsenic was undetectable *in vivo* until the 1830s, and many questions about the element were still unanswered more than 150 years afterwards. The first milestone in arsenic research that Aposhian discussed involves recent insights into arsenic metabolism and the SNPs that can interfere with detoxification of the metabolites formed by biotransformation of the element. These developments are important because, as Aposhian observed, "Inorganic arsenic toxicity is relatively low compared to the toxicity of [the downstream metabolites] MMA(III) and DMA(III)."

According to Aposhian, understanding what enzyme is responsible for the methylation of arsenic species in the human still needs further investigative effort. Arsenic methylation is an important biotransformation pathway in humans and animals that is likely characterized by some enzyme redundancy. The three proposed pathways — involving rabbit-type methyltransferases, CYT 19 and glutathione compounds — are probably all involved, but Aposhian cautioned that until an enzyme can be purified from surgically removed human tissue, the question will remain unanswered.

Aposhian pointed to what he considers the two most important arsenic papers published in the past 25 years. The first, from the Columbia group headed by Joe Graziano, Ph.D., found a significant association between arsenic in drinking water and reduced intellectual function among children in Bangladesh. In the second, an investigative team led by NIEHS Research Pharmacologist Michael Waalkes, Ph.D., reported on a rodent model of inorganic arsenic carcinogenesis in liver, ovary, lung and adrenal glands.

The improved analytical techniques that are now available have made possible identification of the metabolite MMA(III) for the first time in human urine. The Aposhian group's recent acquisition of rapid and sensitive technology has helped the team carry out automated high-throughput speciation analysis.

Although major breakthroughs have taken place in arsenic research and in the development of advanced proteomic methodology, such as Differential Gel Electrophoresis (DIGE), Aposhian concluded that there remain many questions to be answered, ranging from sample collection details to validation procedures. He called for more DIGE global discovery studies, more investigations into cytokines and second messengers, and more studies using surgically removed human tissue.

Return to Table of Contents

Superfund Grantees Engineer Plants to Clean Environmental Pollutants

By Maureen Avakian

In an NIEHS-funded study published in the October 23, 2007 Proceedings of the National Academy of Sciences, University of Washington researchers Stuart Strand, Ph.D., and Sharon Doty, Ph.D., report on their ground-breaking work to transform hybrid poplars with a vector containing rabbit cytochrome P450 2E1. The resulting transgenic plants overexpressed cytochrome P450 2E1, a key enzyme in the metabolism of a variety of halogenated compounds. This modification significantly enhanced the plants' ability to capture and break down volatile environmental pollutants through a process known as phytoremediation.

Superfund researcher Sharon Doty is shown in her lab in the College of Forestry at the University of Washington. (Photo courtesy of Sharon Doty and the University of Washington)

The study grew out of burgeoning interest among environmental scientists in the use of trees to clean up contaminants found at hazardous waste sites. As a result of natural processes fueled by solar energy, trees offer great potential for environmentally sound and cost-effective clean-up of contaminated soil, groundwater and air.

Some tree species, particularly poplars, grow at a remarkable rate – up to 15 feet per year – and their root systems penetrate large volumes of soil. In addition to drawing water and nutrients out of the ground, these trees also take up organic contaminants and metabolize them to harmless products. It is well documented that poplar trees metabolize trichloroethylene (TCE) to innocuous products. There is no release or sequestration of toxic intermediate metabolites such as vinyl chloride, a known carcinogen.

This promising technology of phytoremediation has many advantages over conventional engineering methods such as "pump and treat," including being significantly less expensive, less intrusive and more aesthetically pleasing. The disadvantages of phytoremediation are that the process is often too slow and may be only seasonally effective or remove only small amounts of pollutant from the environment. Regulatory agencies often require significant progress in remediation to be demonstrated in only a few years, making most phytoremediation applications unsuitable.

The team tested the plants' uptake of several environmental pollutants. (Photo courtesy of Sharon Doty and the University of Washington)

Since the 1980's, the NIEHS Superfund Basic Research Program (SBRP) has funded cutting-edge phytoremediation research at the University of Washington. Initiated by the late biochemist Milton Gordon, Ph.D., this work has evolved from identification of plant species best suited to remediation and development of more effective hybrids, to on-going studies to develop a transgenic poplar (*Populus tremula x Populus alba*) with greatly increased rates of metabolism and removal of volatile hydrocarbons including TCE, vinyl chloride, carbon tetrachloride, benzene and chloroform.

In laboratory studies that exposed apical stem cuttings to TCE, the scientists found that CYP2E1-containing transgenic cuttings had average rates of TCE metabolism nearly 45-fold greater than in the control cuttings. Two of the CYP2E1 transgenic lines had TCE metabolism rates that were more than 100-fold higher than in controls. The transgenic cuttings grew normally and did not display any adverse reaction to the TCE or its metabolites.

Strand and Doty then conducted studies to determine if the increased metabolism of TCE in the poplar cuttings led to increased uptake from solution and/or from air. They found that while control cuttings removed < 3 percent of the TCE from hydroponic solution, the CYP2E1 transgenics removed 51 to 91 percent. When exposed to contaminants in the air, the transgenic plants also demonstrated increased uptake. The CYP2E1 plants removed 79 percent of the TCE from the air, while control plants did not show any statistically significant uptake of TCE. In two weeks, the control plants removed an average of only 13 percent of benzene from air, while two CYP2E1 plant lines removed 36 and 46 percent.

The SBRP researchers believe that this work represents the first development of transgenic trees for increased removal of a broad range of serious environmental pollutants from water and air. Additional studies are needed to verify efficacy under field conditions and to ensure that plant tissues do not cause unacceptable impacts on non-target organisms.

Return to Table of Contents

Kastan to Give Falk Memorial Lecture on November 8

By Eddy Ball

The 2007 Hans L. Falk Memorial Lecture Series will feature a talk on November 8 at 2:00 p.m. in Rodbell Auditorium by Michael B. Kastan, M.D., Ph.D. Kastan is Cancer Center director in the Department of Oncology at St. Jude Children's Research Hospital. He will speak on "DNA Damage Response Mechanisms: Implications for Human Disease."

The talk, hosted by Acting Deputy Director Bill Suk, Ph.D., is the twenty-third in the annual series and is part of the NIEHS 2007-2008 Distinguished Lecture Series.

In addition to his work on DNA damage response, Kastan's research interests include molecular oncology and molecular therapeutics, radiation biology, tumor suppressor genes, determinants of chemosensitivity and radiosensitivity, and genetic predisposition and environmental contributions to cancer.

The Hans L. Falk Memorial Lecture Series was initiated by scientists and friends of Falk, the first scientific director at NIEHS, to showcase scientists who have made distinguished contributions to the environmental health sciences. Falk was an internationally known cancer researcher, environmental health science authority, and one of the founding members and shaping forces at NIEHS.

Hans L. Falk Memorial Lecturer Michael Kastan (Photo courtesy of Michael Kastan and St. Jude Children's Research Hospital)

Return to Table of Contents

Registration Open for Superfund Anniversary Meeting

Registration for the Superfund Basic Research and Training Program (SBRP) Annual Meeting "20 Years of Success and a Vision for the Future" is open through November 20. The meeting will take place on December 3-5 at the Washington Duke Inn in Durham.

This meeting will be a celebration of two decades of SBRP accomplishments, a showcase of the program's current contributions and a forum to discuss future directions by identifying emerging technologies and their applications to understanding and mitigating the risks of hazardous waste sites. Since 1987, the SBRP has provided funding to researchers to conduct multidisciplinary studies to address the intractable issues plaguing the national Superfund program.

Return to Table of Contents

Extramural Update

Grant Awards Made for the Genes, Environment and Health Initiative

The National Institutes of Health awarded its first research grants this summer as part of the Genes, Environment and Health Initiative (GEI), a four-year, trans-NIH program that seeks to improve understanding of both the genetic and environmental contributions to complex diseases.

The GEI has two components: an Exposure Biology Program led by NIEHS in partnership with NCI, NHLBI and NIDA for the development of small, portable sensor devices and novel technology to enable more precise measurements of chemical and lifestyle exposures and for the discovery and improved detection of early indicators of biological responses to environmental stressors, and a genetics program led by NHGRI to identify genetic variants in common diseases through genome-wide association studies.

The Exposure Biology Program seeks to improve the understanding of how environmental exposures affect disease risk through the development of tools for improved exposure assessment and more robust measures of biological responses to exposure. In the Environmental Sensors for Personal Exposure Assessment initiative (ES-06-011), researchers will develop field-deployable, wearable devices that can detect exposures to household allergens, gasoline and diesel compounds, fine and ultra-fine particles, and other air pollution components in real-time. Approaches include a color-based sensor array that can detect a wide range of volatile toxicants, personal nasal samplers that can detect inhaled allergens, and an enzymatic activity-based sensor that can detect pesticides, ozone, volatile organic compounds and heavy metals.

The Improved Measures of Diet and Physical Activity initiative (CA-07-032) will develop tools for accurate measurements of diet and physical activity, including collecting detailed data on consumption of food, beverages and dietary supplements with food records, 24-hour dietary recalls and direct measurements of physical activity using heart rate monitoring and motion sensors. Among the approaches being developed are Web-based multimedia tools for reporting dietary intake among children, a mobile telephone food record coupled with image processing software to estimate nutrient intake and an accelerometer-enabled cell phone with GPS capability that can transmit physical activity data in real time.

A third initiative, Field-Deployable Tools for Quantifying Exposures to Psychosocial Stress and Addictive Substances (DA-07-005) supports the development of tools that can detect and quantify personal exposure to such psychosocial stressors as crowding or isolation, discrimination, traumatic events, loss of job, family violence, deprivation, or adverse social environments and to exposure to addictive substances such as nicotine, alcohol, cannabis, stimulants and opiates.

The Biological Response Indicators of Environmental Stress initiatives (ES-06-012 and ES-06-013) will promote the development of robust biomarkers or signatures that reflect changes in biological pathways following exposure to environmental stressors. These biomarkers reflect changes in key pathways, such as inflammation, oxidative stress, DNA damage, endocrine disruption and epigenetic regulation, which are known to be influenced by environmental stressors. Examples of the research approaches include identifying protein biomarkers of exposure to pesticides and tobacco smoke, gene-expression markers of airway response to tobacco smoke, and genomic and metabolomic signatures of alcohol-induced liver damage.

The research projects in the Exposure Biology Program will develop tools for more precise measures of exposure and response that will begin to pave the way toward the overarching goal of the GEI initiative of understanding the interaction between genetic and environmental factors that contribute to disease.

Studies within the genetics component of the GEI will identify genetic differences between cases and controls in common diseases, including heart disease, type 2 diabetes and lung cancer. Applications for additional genetics studies were recently solicited (HG-07-012). Two genotyping facilities, at the Broad Institute in Cambridge Massachusetts and at Johns Hopkins University in Baltimore, have been funded, as well as a coordinating center at the University of Washington in Seattle. Another initiative (HL-07-010) has recently funded projects to develop improved methods for analyzing gene-environment interactions in complex diseases.

Return to Table of Contents

For More Information on the GEI Program

- Visit the NIH Genes, Environment and Health Initiative Website.
- Contact a program administrator:

NIEHS
David Balshaw, Ph.D.,
Daniel Shaughnessy, Ph.D.

NCI
Jill Reedy, Ph.D.

NHLBI
Cay Loria, Ph.D.

NIDA
Kay Wanke, Ph.D.

Extramural Papers of the Month

By Jerry Phelps

Safety Oversight among Contract Workers not Equal to DOE Workers

Recent NIEHS-funded research on safety and health programs within the Department of Energy (DOE) found that hiring contractors often provides specialized knowledge in solving a problem, but also can bring "young, inexperienced, inadequately trained workers onto industrial and hazardous waste sites."

The researchers found that reliable data on subcontractor health and safety programs are limited. They also found that DOE has first-rate safety standards, but that these standards are not always adhered to by contract workers, making for unsafe work conditions in some instances. They point out that DOE is increasing agency efforts toward enhancing contractor protection, but that there are lucrative financial incentives for productivity that are not offset by "disincentives for unsafe work practices."

The report points out that these findings are probably not unique to DOE because of the increased national and international trends for outsourcing of work traditionally done by direct hires. The research team recommends that "site hosts" such as DOE maintain stringent oversight of safety and health programs for all workers by working with contractors at all levels to value safety of workers above all other considerations and that contracting should not be viewed as a means of lessening the liability of the owners of hazardous waste sites and facilities.

Citation: Gochfeld M, Mohr S. Protecting contract workers: case study of the US. 2007. Department of Energy's nuclear and chemical waste management. Am J Public Health 97(9):1607-1613.

Return to Table of Contents

High Blood Urate Levels Linked to Lower Risk of Parkinson's Disease

A large-scale prospective epidemiologic study investigating the link between plasma urate levels and the risk of Parkinson's disease conducted by NIEHS-funded researchers shows that the higher the urate level, the lower the risk of the progressive neurodegenerative disease.

The researchers used a cohort of more than 18,000 men who were participating in the Harvard-based Health Professionals Follow-up Study, which began in 1986. Blood samples were drawn between 1993 and 1995, and the subjects' health status has been followed since.

Men with plasma urate concentrations in the top 25 percent exhibited 55 percent lower risk of developing Parkinson's disease over the course of the study than men in the bottom 25 percent. These results mirror those seen in two previous yet smaller studies.

The research team hypothesizes that the antioxidant properties of urate may be the cause of the decreased risk. Oxidative stress is thought to contribute to the progressive loss of dopamine producing neurons in Parkinson's cases. To follow-up on this finding, two of the researchers are collaborating on the design of a clinical trial in Parkinson's disease patients to determine whether elevating levels of urate may slow the progression of the disease.

Citation: Weisskopf MG, O'Reilly E, Chen H, Schwarzschild MA, Ascherio A. 2007. Plasma urate and risk of Parkinson's disease. Am J Epidemiol 166(5):561-567.

Return to Table of Contents

Solid Waste Facilities in N.C. Disproportionately Located in Communities of Color

Landfills and other solid waste facilities are twice as likely to be located in communities of color in North Carolina, according to new NIEHS-funded research findings reported in the September 2007 issue of *Environmental Health Perspectives*.

A research team from the UNC School of Public Health examined records for all solid waste facilities in North Carolina as of 2003 and found that 419 facilities were permitted as of the end of 2003. Facilities were 2.1 times more likely to be found in communities with greater than 10 percent people of color. The research also found that facilities were 1.4 times more likely in communities with average home values less than $100,000.

Newer facilities permitted between 1990 and 2003 were 2.2 times more likely to be found in communities with populations made up of greater than 10 percent minorities. Numbers were similar for private versus public facilities.

The communities that host these facilities are concerned about their health and well being because of truck traffic and traffic-related pollution, odor, noise and water contamination. Other concerns include the effect on property values and the effects these facilities have on the location of schools, medical facilities and cleaner industries.

Citation: Norton JM, Wing S, Lipscomb HJ, Kaufman JS, Marshall SW, Cravey AJ. Race, wealth, and solid waste facilities in North Carolina. 2007. Environ Health Perspect 115(9):1344-1350.

Return to Table of Contents

Epigenetics vs. Gene Mutations in Colorectal Cancer

A large research team at John's Hopkins University led by NIEHS grantee Stephen Baylin has developed a new method they term a "transcriptome-wide approach" to identify genes susceptible to hypermethylation and transcriptional silencing in human colorectal cancer.

Using microarray technology, the new approach enables the identification of genes silenced by promoter hypermethylation and identifies candidate cancer genes in single tumors with a high degree of accuracy. The team estimates that nearly 5% of all known genes may be methylated in individual tumors. They found more hypermethylated genes than mutated genes in tumor tissue.

The study data indicate that for any cancer, failing to screen for both genetic and epigenetic changes may result in underestimating the full range of gene alterations and subsequent cellular pathway abnormalities. The overall findings point towards the need for genome-wide cancer gene screening efforts to include studying hypermethylated genes. These genes should be prioritized for sequencing to find mutations as well as prioritizing newly discovered mutations to be analyzed for methylation.

Citation: Schuebel KE, Chen W, Cope L, Glockner SC, Suzuki H, Yi JM, Chan TA, Van Neste L, Van Criekinge W, van den Bosch S, van Engeland M, Ting AH, Jair K, Yu W, Toyota M, Imai K, Ahuja N, Herman JG, Baylin SB. 2007. Comparing the DNA hypermethylome with gene mutations in human colorectal cancer. PLoS Genet 21;3(9):1709-1723.

Return to Table of Contents

Intramural Papers of the Month

By Robin Arnette

S-nitrosoglutathione Reductase Linked to Childhood Asthma

In an NIEHS-funded study published in the *Journal of Allergy and Clinical Immunology*, researchers from NIEHS, working with their collaborators at the Mexican National Institute of Public Health and the Hospital Infantil de México Federico Gómez, found a relationship between genetic polymorphisms in S-nitrosoglutathione reductase (GSNOR) and childhood asthma.

GSNOR controls intracellular levels of S-nitrosothiols—endogenous bronchodilators—by catalyzing the metabolism of S-nitrosoglutathione (GSNO). Scientists had suspected that since S-nitrosothiol levels were reduced in airway lining fluid taken from asthmatics, S-nitrosothiols conferred some protection against asthma in response to allergens.

The team, using DNA samples from 532 asthmatic children and their parents in Mexico City, Mexico, genotyped seven single nucleotide polymorphisms (SNPs) in GSNOR. Two of the seven SNPs were associated with asthma risk: rs1154404 and rs28730619. The common minor A allele of rs1154404 conferred a decreased risk of asthma while the higher frequency minor G allele of rs28730619 conferred an increased risk.

Although recent research from another group implicated GSNOR in asthma etiology in mouse studies, this publication was the first to demonstrate the connection in humans. This work was highlighted as a Scientific Breakthrough of the Year at the 2007 American Thoracic Society International Conference.

Citation: Wu H, Romieu I, Sienra-Monge JJ, del Rio-Navarro BE, Anderson DM, Jenchura CA, Li HL, Ramirez-Aguilar M, Lara-Sanchez ID, London SJ. 2007. Genetic variation in S-nitrosoglutathione reductase (GSNOR) and childhood asthma. J Allergy Clin Immunol 120(2):322-328.

Return to Table of Contents

Genes Associated with Murine Exercise Endurance

NIEHS researchers in collaboration with investigators from the University of North Carolina-Charlotte and Johns Hopkins University have identified quantitative trait loci (QTLs) associated with maximal exercise endurance in mice. The findings were published in the *Journal of Applied Physiology*.

The team mated Balb/cJ, a mouse strain that exhibited high exercise endurance (HEE), with DBA/2J, a strain that exhibited low exercise endurance (LEE). The resulting F_2 progeny were tested on a treadmill to determine exercise endurance and were identified as either HEE or LEE. The researchers genotyped the mice and found two QTLs linked to maximal exercise endurance: *EEX* existed on the X chromosome and $EE8^F$ appeared on chromosome 8. Of the two, $EE8^F$ was sex-linked, being found in female mice, and the one that had more sequence identity with human and rat QTLs previously linked with exercise endurance.

Physical exercise has been proven to reduce hypertension and incidences of heart disease and stroke in humans, but an individual's aerobic capacity is largely determined by genes. This research has narrowed the genetic linkages involved in exercise endurance and serves as a starting point for further analysis of the genetic factors that influence this phenomenon.

Citation: Lightfoot JT, Turner MJ, Knab AK, Jedlicka AE, Oshimura T, Marzec J, Gladwell W, Leamy LJ, Kleeberger SR. 2007. Quantitative trait loci associated with maximal exercise endurance in mice. J Appl Physiol 103(1):105-110.

Return to Table of Contents

Proteasomes, Pol II and Glucocorticoid Receptors in Transcription

In an NIEHS-funded study published in the July issue of *Molecular and Cellular Biology*, researchers from the Chromatin & Gene Expression Group in the Laboratory of Molecular Carcinogenesis offered an additional role for the proteosome: transcriptional involvement in regulating receptor-mediated gene expression.

The 26S proteasome, a biological macromolecule present in eukaryotic cells, is responsible for degrading "misfolded" or damaged proteins. The proteasome also participates in, or regulates, transcriptional processes including that by the hormone-dependent glucocorticoid receptor (GR). When a proteasome-specific inhibitor prevents GR degradation, researchers see an increase in GR-mediated gene transcription.

Using the mouse mammary tumor virus (MMTV) promoter as a model, the researchers used a variety of molecular techniques such as chromatin immunoprecipitation (ChIP) and RNA interference (RNAi), to determine the mechanisms mediating the hormone-dependent increase in transcription following proteasome inhibition. ChIP analysis revealed that after proteasome inhibition, GR loading on the MMTV promoter decreased. Chromatin analysis and RNAi experiments demonstrated that the proteolytic core of the proteasome supported a more efficient transcriptional elongation. Taken together these data suggested that, in mammals, GR-mediated transcription and proteasome activity were linked to modifications in chromatin and of the RNA polymerase II (Pol II) machinery.

Citation: Kinyamu HK, Archer TK. Proteasome activity modulates chromatin modifications and RNA polymerase II phosphorylation to enhance glucocorticoid receptor-mediated transcription. 2007. Mol Cell Biol 27(13):4891-4904.

Return to Table of Contents

The Benefits of Using Risk-based Sampling

Researchers from NIEHS and Westat detailed the statistical power advantages of using risk-based sampling for prospective studies of etiologic factors. The report was published in the *American Journal of Epidemiology* and used as illustration the Sister Study.

In a prospective study using risk-based sampling, researchers recruit siblings (or other first degree relatives) of affected individuals and follow them for a period of time. It is generally believed that prospective studies have fewer biases than retrospective case-control studies, for example, because retrospective studies target individuals who have already had the disease, which tends to distort findings. Risk-based sampling can make a prospective study more feasible by increasing the number of new cases of the disease of interest that will accrue over time. Additional statistical advantage comes from the fact that the siblings of affected individuals will have increased prevalence of both risk-related genetic variants and potentially relevant exposures that tend to occur in families. An added benefit is the fact that risk-based sampling can produce motivated volunteers, which will enhance response rates and participation over time.

The team illustrated the additional statistical power gained with different assumptions about allele and exposure frequency under different models of inheritance, and demonstrated that this design has increased power to identify exposure effects, gene effects, and interactions under most models. Of note, the design increases the power to detect environmental effects when there are gene-environment interactions, even when the gene involved is not known.

Citation: Weinberg CR, Shore DL, Umbach DM, Sandler DP. 2007. Using risk-based sampling to enrich cohorts for endpoints, genes, and exposures. Am J Epidemiol 166(4):447-455.

Return to Table of Contents

NIEHS
National Institute of
Environmental Health Sciences

The e-Factor, which is produced by the Office of Communications and Public Liaison, is the staff newsletter at the National Institute of Environmental Health Sciences. It is published as a communication service to NIEHS employees. We welcome your comments and suggestions. The content is not copyrighted. It can be downloaded and reprinted without permission. If you are an editor who wishes to use our material in your publication, we ask that you send us a copy for our records.

• Director of Communications: Christine Bruske
• Writer-Editor: Eddy Ball
• Science Editor: Robin Arnette