eFactor
Your On-Line Source for NIEHS News

July 2007

NIEHS Spotlight

Science Notebook

Inside the Institute

NIEHS Spotlight

NIEHS Spearheads Epigenetics Roadmap Initiative

By Eddy Ball

On May 30, NIEHS Director David A. Schwartz, M.D., announced that NIH had selected as part of its Roadmap the Epigenetics Initiative prepared by NIEHS in partnership with the National Institute on Drug Abuse (NIDA). Schwartz summarized this project during his report to the National Advisory Environmental Health Sciences Council during its spring meeting in Rodbell Auditorium. The Initiative marks the first time that NIEHS has played such an important role in shaping the NIH Roadmap.

Senior Science Advisor Brenda Weis, Ph.D., gave the council an overview of the trans-NIH initiative. "In typical Roadmap fashion," she said, "we assembled and led a trans-NIH Working Group.… The charge to the group was to develop a compelling research program that would transform biomedical research in the next ten years." What emerged is a comprehensive proposal for realizing coordination, standardization, integration and leadership in the field of epigenetics to facilitate translation of research into clinical applications.

The funding for the Initiative will span a ten year period from fiscal year (FY) 2008 through FY 2017 and could involve between $129.5 and $248.5 million in grants,

"We'll play a major role in rolling this initiative out," Schwartz explained. "This is a very exciting development for the Institute." (Photo courtesy of Steve McCaw)

The Microbiome Initiative

The Microbiome refers to the full collection of microbes (bacteria, fungi, viruses, etc.) that naturally exist within the human body. According to the authors of "Extending Our View of Self: the Human Gut Microbiome Initiative (HGMI)," the adult body typically harbors ~10 times more microbial than human cells, and the distal gut by itself contains up to 100 trillion bacterial cells. Scientists in the field speculate that the human genome could be seen as an amalgam of human genes and the genes of our microbial 'selves.' "Without understanding the interactions between our human and microbial genomes," the authors argue, "it is impossible to obtain a complete picture of human biology."

Initiatives in this area would focus on developing a deeper understanding of these communities of microbes in order to determine how they affect human health. The Roadmap 1.5 Initiative is being led by National Institute of Allergy and Infectious Diseases Director Anthony Faucci, M.D., and Human Genome Research Institute (HGRI) Director Francis Collins, M.D., Ph.D.

While NIEHS was not instrumental in this initiative, the Institute collaborated with HGRI in a special presentation on the Human Microbiome Project at the annual meeting of the American Society for Microbiology in Toronto on May 24. "Our [institute's] interest in the Microbiome is in the toxins released by these microorganisms," Schwartz observed. "The question [for NIEHS] is 'How do we hook into that initiative in a meaningful way?'"

Three additional initiatives, Inflammation, Phenotyping and Protein Capture, were not approved during the first round, but they may be approved later as scaled-down versions.

depending on which version of the program proposal is approved by the NIH Office of Portfolio Analysis and Strategic Initiatives (OPASI). The program includes Roadmap co-funding of up to 15 Institute and Center (IC)-based programs over the ten year period and a $4 million "jump start" allocation in FY 2007.

Following a review of proposals by the 27 NIH IC directors on May 18, the Epigenetics Program, along with a Microbiome Program, was approved for Roadmap 1.5 support. Funding for the Epigenetics Initiative and the Microbiome Initiative (see text box) will come from what is known as the Common Fund, a repository to which each IC contributes annually.

Being a part of the NIH Roadmap recognizes a research area as one of "the most pressing problems facing medical research today that can be uniquely addressed by the NIH as a whole." While funding for a Roadmap initiative will not affect an individual institute's budget beyond its contribution to the Common Fund, the Roadmap itself is subject to the same budget pressures as the rest of the NIH.

Senior Science Advisor Brenda Weis. Schwartz said of the NIEHS representatives on the Working Group, "This program would not have happened had it not been for the dedication of Brenda and her staff and associates [Heindel and Tyson]." (Photo courtesy of Steve McCaw)

As Weis observed in her presentation, epigenetics is an emerging science with nearly 5,000 studies related to epigenetics and its connection to disease published in 2006. The term refers to potentially heritable traits that occur as early as *in utero* and are not dependent on DNA sequence. These traits have been strongly implicated in cancer and tumor formation and linked to a variety of other conditions, ranging from obesity and diabetes to impairments in memory and learning.

According to Weis, although interest the role of epigenetics in cancer has surged in recent years, research in the field suffers from infrastructure weaknesses, lack of organization and thus far limited focus. The Roadmap 1.5 Epigenetics Initiative, Weis explained, is designed to help this emerging area of science by pursuing four enabling objectives to expand disease-focused research:

- Establishing an NIH-led international consortium as part of the $4 million "jump start" allocation
- Creating references for the field by developing "maps" for 24 epigenomes in human embryonic stem cells, differentiating and differentiated cells, cell lines and tissue (5 year)
- Building a publicly accessible epigenetic database through collaboration with the National Library of Medicine's National Center for Biotechnology Information to develop a computational infrastructure (2 year) integrated with existing public data sources (10 year)
- Developing and enhancing technology to identify standard protocols, technology platforms, and reagents for maintenance of stem cells/tissues and epigenetics, including antibodies (10 year)

Schwartz and NIDA Director Nora Volkow co-chaired the trans-NIH Epigenetics Working Group. Weis, along with Extramural Administrators Jerry Heindel, Ph.D., and Fred Tyson, Ph.D., represented NIEHS on the 36-member group.

Return to Table of Contents

Advisory Council Meeting: An Engaging Discussion

By Eddy Ball

As the first morning of the spring meeting of the Council came to a close on May 30, a remark by member John Essigman, Ph.D., captured the essence of the day and a half event. "This is the most interesting council meeting I've ever been to," Essigman said as the Council adjourned for lunch after a morning of engaging discussion between Council members and NIEHS representatives.

By the time the meeting adjourned the next day, Council members had weighed-in on six reports and concept clearances, giving four their whole-hearted support. A report on funding the Children's Health Centers and a Concept Clearance proposal on a Global Environmental Health Initiative prompted Council members to share additional insights from their own experiences and expertise.

Council members expressed overwhelming support for the work underway in Biodefense Research at NIH and NIEHS, as reported by Ernie Takafuji, M.D., director, Office of Biodefense Research Affairs, National Institute of Allergy and Infectious Diseases. The trans-NIH effort, called the CounterACT program, promotes product-directed research into ways to improve the country's defense against bioterrorism.

The program funds research into interventions for chemical injury and the long-term sequelae of bioterrorism, rapid assessment of injuries, and early

Few of those who attended the opening session will forget MIT Professor John Essigman's assessment of the Council meeting. (Photo courtesy of Steve McCaw)

Two Initiatives on Hold

The first report Council heard during its spring meeting was presented by Consultant Daniel Krewski, Ph.D., on proposed changes by the working group he headed to funding mechanisms for the Children's Environmental Health Centers. Reviewer Joseph Graziano, Ph.D., called a proposal for limiting center funding for these programs, as the Working Group suggested, in favor of RO-1 funding, "very problematic." Center funding, he noted, gives grantees a greater degree of flexibility than directed funding and allows researchers to re-focus their work based on preliminary findings.

Earlier in the meeting, Schwartz had reassured Council that "We are fully committed to supporting research efforts in children's environmental health… [and] we are really interested in continuing this partnership with the EPA [Environmental Projection Agency]." The group wanted to make sure that this commitment extended to the current funding mechanism for the research network and the highly successful community-based approach in the programs.

At the suggestion of group members Daniel Liebler, Ph.D. and David Christiani, M.D., the group tabled until its September meeting a DERT Global Health Initiative Concept Clearance that it considered too general. Presenter William Suk, Ph.D., was commended by Reviewer Peter Spencer, Ph.D., for offering NIEHS "an extremely important initiative [and] an opportunity for extraordinary research discovery as well as contribution."

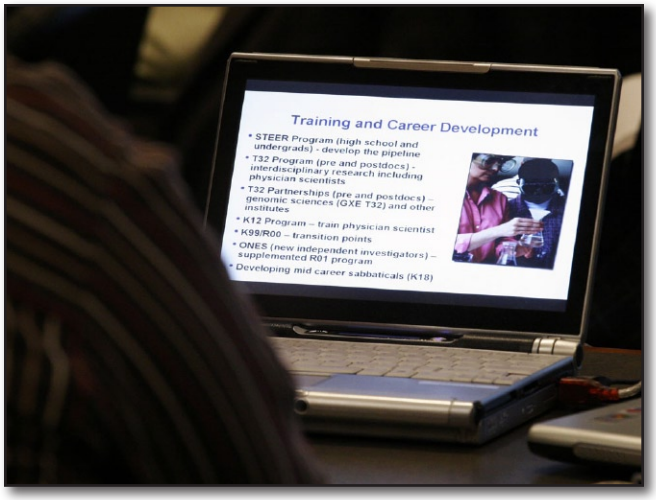
Although several members echoed Spencer's sentiments, the group still wanted more information about the way the proposal would affect spending priorities, how it would realize public/private partnerships, and specific programmatic details. In her comments about the initiative, member Kathleen Dixon, Ph.D., cautioned that doing more preliminary work could easily make the difference between the project's success and failure.

detection of the pathogens and hazardous chemicals used in attacks. The NIEHS contribution is being directed by Elizabeth Maull, Ph.D., program administrator in the DERT Susceptibility and Population Health Branch. Thus far, the program has funded 23 requests for applications and four Centers of Excellence nationwide.

The Council also unanimously approved the concept of an NIH NanoHealth Initiative presented by Assistant to the Deputy Director Sally Tinkle, Ph.D. Spearheaded by NIEHS, the initiative proposes an integrated, interdisciplinary program addressing critical research needs for the safe development of the nanoscale materials and devices that are increasingly a part of everyday life.

The initiative, Tinkle explained, draws upon the resources of NIH institutes and centers to improve understanding of engineered nanomaterials (ENM) science, biological response to ENM and diseases that may be induced by exposure. A fourth component of the initiative would involve development of advanced training programs within the context of established NIH grants and programs, as well as in joint efforts with public and private organizations.

Members of the Council also applauded the Concept Clearance proposal for a new Undergraduate Diversity Training Program in Environmental Health Sciences presented on May 31 by Mike Humble, Ph.D., of the DERT. Humble, a health science administrator in the Cellular, Organ and Systems Pathobiology Branch, is working with colleagues Branch Chief Pat Mastin, Ph.D., and Carol Shreffler, Ph.D., to recruit participants for the summer 2008 award date.



The May 30-31 event was also of interest as the first "paperless" Council meeting, thanks to the efforts of DERT Program Administrator Liz McNair. (Photo courtesy of Steve McCaw)

NIAID scientist Ernie Takafuji used some provocative graphics to underscore the importance of the trans-NIH CounterACT Initiative. (Photo courtesy of Steve McCaw)

University of Washington Professor Elaine Faustman expressed the Council's consensus opinion when she lauded the Undergraduate Diversity Training Program in Environmental Health Sciences as a good fit for the Institute. (Photo courtesy of Steve McCaw)

According to Humble, the program will operate under a T34 funding mechanism used by other institutes. It will support minority college students in their junior and senior years with mentoring and provide financial support for students and for curriculum development at participating institutions. Reviewer John Essigman, Ph.D., described the proposal as "a great idea for keeping the pipeline [of new scientific talent] full," and Reviewer Elaine Faustman, Ph.D., commented that the program "fits extremely well" with existing diversity programs at NIEHS.

Columbia University Associate Dean for Research Joseph Graziano objected to Working Group recommendations on funding for Children's Environmental Health Centers. (Photo courtesy of Steve McCaw)

Despite enthusiastic support by Oregon Health & Science University Professor Peter Spencer, the Council decided to delay consideration of the Global Environmental Health Initiative. (Photo courtesy of Steve McCaw)

Return to Table of Contents

John Bucher Chosen to Head NTP

By Eddy Ball

On June 15, NIEHS announced the appointment of toxicologist John Bucher, Ph.D., as associate director of the National Toxicology Program (NTP). Bucher has been a part of the NTP for 24 years, most recently as deputy director of the Environmental Toxicology Program and chief of its Toxicology Operations Branch.

Selected from a group of 33 qualified applicants for the position, Bucher began his new duties on June 18, as the program started a process of realignment within the Institute's Division of Intramural Research (DIR). He succeeds Allen Dearry, Ph.D., who served as acting associate director from January 2006 to June 2007.

In announcing the choice, NIEHS Director and Director of the NTP David A. Schwartz, M.D., praised Bucher as a scientist with "outstanding scientific credentials, an insightful vision for toxicological research and an in-depth knowledge of the NTP." Schwartz expressed his confidence in Bucher's ability to realize the goals of the NTP Vision and Roadmap for the 21st century, which the new associate director was instrumental in developing.

Bucher joined the NTP in September 1983 after completing his Ph.D. in Pharmacology at the University of Iowa and a postdoctoral fellowship at Michigan State University. He has served as chief of the Toxicology Operations Branch for the past 11 years and deputy

NTP Associate Director John Bucher was able to celebrate two pieces of good news on June 15 — his appointment as associate director and the birth of his first grandchild. (Photo courtesy of Steve McCaw)

director of the Environmental Toxicology Program since 1995. Bucher received his certification as a diplomate by the American Board of Toxicology in 1984.

During his tenure at NTP/NIEHS, Bucher has published over 100 studies in peer-reviewed journals and played a key role in shaping the program's research and policies, including comprehensive studies of dioxin and dioxin-like chemicals, chemicals that mimic estrogens and, more recently as one of the pioneers in the field, manufactured nanomaterials. Bucher's leadership was important in the development of the NTP Center for the Evaluation of Risks to Human Reproduction.

"I look forward to working with our exceptionally talented staff and NTP partners to produce the quality data and scientific understanding necessary for the protection of public health and critical to the further evolution of the science of toxicology," said Bucher. "I am honored to follow in the footsteps of the truly outstanding individuals who have led this program in the past."

According to Schwartz, realignment of the NTP within DIR will help it achieve higher visibility and greater efficiency. "Our goal is to closely coordinate NTP and DIR research so we can make the most of our resources and have an even greater impact on safeguarding public health," Schwartz said.

Return to Table of Contents

Schwartz Tapes Television Show on Exposure Biology Devices

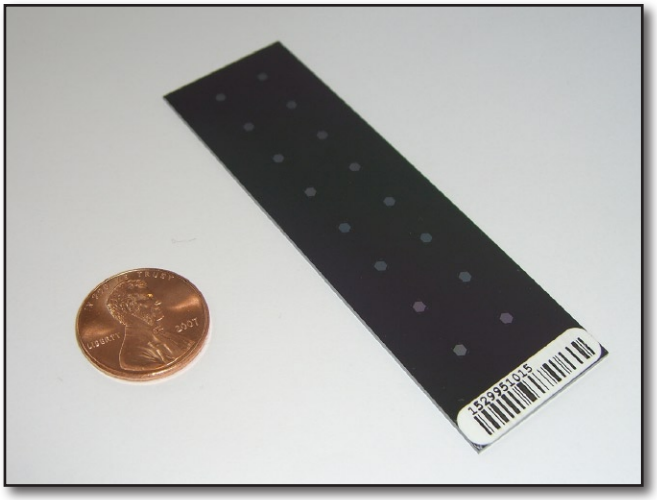
By Eddy Ball

NIEHS Director David A. Schwartz, M.D., and NIH grantee David Walt, Ph.D., joined NIH Director Elias Zerhouni. M.D., on June 4 to tape a segment of the Medical Broadcasting Channel (MBC) program "Tomorrow's Medicine Today." Filming took place in studios at New Jersey's Montclair State University. Clinical psychiatrist Naomi Weinshenker, M.D., of New York University co-hosted the 30-minute segment with Zerhouni. The show featured discussions of current biomedical research advances in exposure biology and insight into the ways NIH affects people's lives.

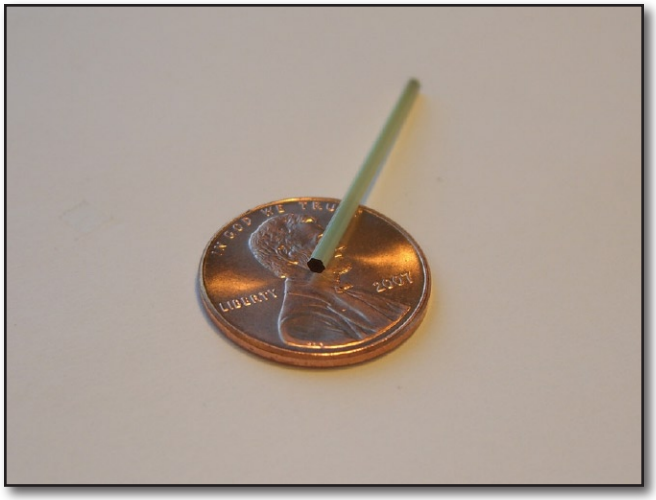
The segments will be broadcast worldwide over MBC via satellite and internet transmission to some 23 million health care workers. Although the series has yet to be scheduled for wider broadcast in the United States, the producers anticipate that New Jersey Public Television will pick up the series and then syndicate it around the country.

During his part of the show, Schwartz discussed the gene-environment connection to many diseases and chronic conditions, such as allergies, asthma, Parkinson's and obesity, and the rationale behind the NIEHS Exposure Biology Program. According to Schwartz, the technologies developed with Exposure Biology grants will help to measure people's exposure to agents in their environment and lead to a better understanding of an individual's biological response to those environmental agents.

New devices promise significant advances over current technology that can only measure one agent, such as formaldehyde, Schwartz explained. Devices now in development will be capable of making many environmental measurements simultaneously. With this detailed information about an individual, physicians will have an opportunity to design a truly personalized medicine, and researchers will have access to the data they need to understand better the links between exposure, genes and disease.



Walt's lab utilizes small chips for the monitoring devices, which house small arrays containing thousands of features. (Photo courtesy of David Walt and Tufts University)



Together with small chips, the tiny fibers used in the devices make it much easier for individuals to carry monitors around with them. (Photo courtesy of David Walt and Tufts University)

Walt, a professor of Bioorganic and Materials Chemistry at Tufts University and Howard Hughes Medical Institute, has been working on smaller and more sophisticated environmental monitors with grants from National Institute of Dental and Craniofacial Research and the National Institute of Biomedical Imaging and Bioengineering. These new monitors can conduct millions of experiments and collect millions of measurements of the environment and a person's biological reactions using very small clinical samples.

The most advanced of these biosensors utilize tiny microarrays, fiber optics, and microfluidic chips for protein and peptide separations. As the devices get progressively smaller and economy of scale begins to affect material costs, the monitors are becoming more affordable and easier for people to carry with them. The monitors can alert health care practitioners of an individual's exposure to an agent and identify the link between a symptom, such as wheezing in an asthmatic, and the specific agent, such as cat dander, that caused it. With information from the biosensors, researchers can study fundamental aspects of biochemistry, genetics, cell biology and olfaction.

MBC broadcasts medical education content all around the world 24 hours a day, seven days a week, airing both donated and original medical video content to help educate physicians and other allied healthcare workers on both satellite and Internet2. The network is a division of Medical Missions for Children, which describes itself as a four-star, multiple-award winning charity located at St. Joseph 's Children's Hospital in Paterson, NJ.

Return to Table of Contents

Alicia Moore Awarded for EEO Contributions

By Lillian Gu

Alicia Moore received the 2007 NIH Harvey J. Bullock, Jr. Award for Equal Employment Opportunity Achievement on June 13 in Bethesda, Md. Only one employee out of the 27 Institutes and Centers is chosen each year for "significant contributions in furthering equal opportunity."

A biologist in the Comparative Pathobiology Group in the Laboratory of Experimental Pathology, Moore has been actively involved in promoting equal opportunity since she started working at the NIEHS 16 years ago. However, when a flare of lupus in 2001 weakened her legs and confined her to a wheelchair, Moore's first-hand experience with disability brought her commitment to equal opportunity to another level, inspiring her to help establish the Disability Advocacy Committee (DAC) in May 2005.

"I think it's important that people are aware of the various issues related to diversity and disability. I believe that knowledge is wealth," asserted Moore, who is currently the Chair of DAC.

Biologist Alicia Moore (Photo courtesy of Steve McCaw)

NIEHS Trans-NIH Group Award Winners

At the 2007 NIH Director's Awards Ceremony, 15 other NIEHS employees were honored for their exceptional contributions to the achievements of trans-NIH Roadmap for Medical Research working groups.

Medical Countermeasures Against Toxic Chemicals Team

- Dennis Lang, Ph.D., Acting Director, Division of Extramural Research and Training (DERT)
- Elizabeth Maull, Ph.D., Program Administrator, DERT Susceptibility and Population Health Branch

NIH Information Security Team

- Charlie Davis, Network Infrastructure Manager, Lockhead-Martin Information Technology (LMIT)
- Jim Dix, Electronics Engineer, Office of Management Computer Technology Branch (OM/CTB)
- Nancy Feder, Security Function Lead, LMIT
- Matt Jordan, Security/System Administrator, LMIT
- Rob Levine, Computer Specialist, OM/CTB
- Gary Rodgers, ITSS Program Manager, LMIT
- Nancy Stegman, Chief, OM/CTB
- Charlie Tate, Electronics Engineer, OM/CTB

Clinical and Transitional Science Award Program Team

- William Martin. M.D., Director for Translational Research, Office of the Director (OD)
- Carol Shreffler, Ph.D., Health Administrator, DERT Cellular, Organ and Systems Pathobiology Branch

Molecular Libraries and Imaging Project and Development Team

- David Armstrong, Ph.D., Acting Chief, Laboratory of Neurobiology, Division of Intramural Research (DIR)
- Christopher Portier. Ph.D., Associate Director for Risk Assessment, OD
- Raymond Tice, Ph.D., Toxicology Operations Branch, Environmental Toxicology Program, DIR

A spin-off of the NIEHS Diversity Council, DAC provides a support network for employees and visitors with disabilities at NIEHS and helps to improve the employment, conditions and quality of life of employees with disabilities and visitors to the NIEHS facilities. Under Moore's leadership, DAC has headed up several efforts to improve accessibility and eliminate communication barriers for those with disabilities. DAC currently has 15 active members.

DAC members have only good things to say of Moore. "She brings her skills as a scientist and that logical, rational process. Not only is she driven, she's also incredibly rational and organized," commented EEO Specialist Virginia (Ginny) Ivanoff, NIHOD Office of Equal Opportunity (OEO).

"It takes a special person to lead the group, and I think Alicia has done a tremendous job of following up with meetings, keeping us on track, making sure that things get done," added EEO Specialist Gerard Roman, NIHOD OEO.

DAC hosted the first annual "Disability Awareness Month" in October 2006, which turned out to be a success. This year's theme will be "Workers with Disabilities: Talent for a Winning Team." The DAC has planned several events that will be of interest to many employees at NIEHS.

Return to Table of Contents

Extramural Grantee Gets Funding for Clinical Trials

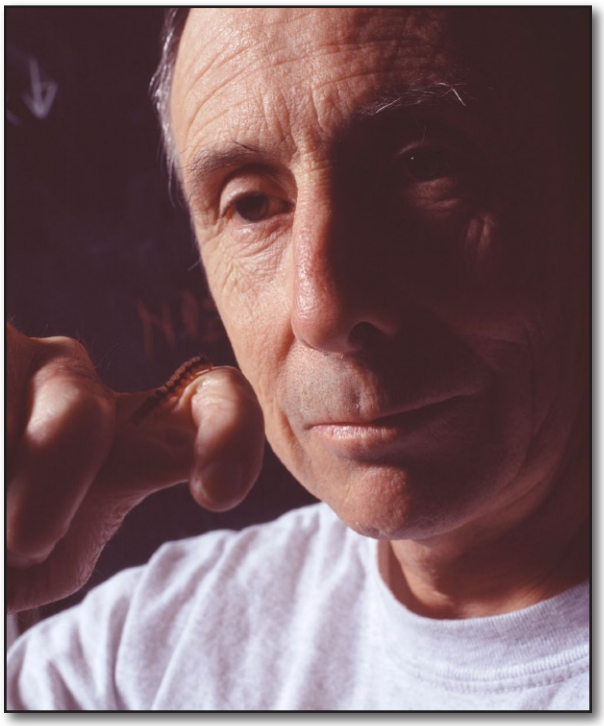
By Eddy Ball

Long-time Extramural Grantee Bruce Hammock, Ph.D., recently received the kind of good news researchers long to hear. Arête Therapeutics, Inc., a privately held biopharmaceutical company, announced in May that it had raised $35 million in venture capital to initiate clinical trials for a family of compounds developed by Hammock. During discovery-phase studies, the compounds showed considerable promise for effective treatment of hypertension and inflammation.

This latest influx of investment brings the total Series A funding for developing Hammock's discovery to $51 million. Arête anticipates beginning a phase 1a/1b clinical trial for its soluble epoxide hydrolase (sHE)-inhibitor-based Investigational New Drug (IND) candidate, currently dubbed AR9281, by the end of the year.

Hammock is a distinguished professor at the University of California at Davis and a prolific researcher who has received NIEHS grants since 1973. He is director of the NIEHS-UC-Davis Superfund Basic Research Program.

Hammock's research into the basic biology of how caterpillars turn into butterflies led to discoveries about the novel enzyme and its relationship to several disease conditions in mammals.



For Hammock, caterpillars, such as the one on his finger, turned out to be the source of inspiration for the process that may be "the first new target for hypertension in twenty years." (Photo courtesy of Bruce Hammock and the University of California at Davis)

Hammock found that inhibiting the action of sEH blocked the breakdown of fatty acids in the epoxygenese branch of the arachidonic acid cascade. These fatty acids, called epoxy-lipids, have vasodilation and anti-inflammatory effects that can help restore the balance of fatty acids — and counter the influence of the products of the arachidonic cascade that promote inflammation, pain and hypertension.

"The practical success of this work is a testament to the value of fundamental science," Hammock observed in the press release from Arête. "This work started asking about the basic biology of how insect caterpillars turn into butterflies, and now may lead to a valuable new class of molecules for treating serious human disease."

Hammock has repeatedly acknowledged the importance of NIEHS support in his research into sEH and sEH inhibition. During his Distinguished Lecture at NIEHS in October 2006, he said, "The work has been funded probably 10 percent by the Department of Agriculture and 90 percent by the NIEHS [Superfund Basic Research Program]."

Among Hammock's more than 650 peer-reviewed publications are a series of collaborations with NIEHS colleagues, including Senior Scientist Darryl Zeldin. One of their studies identifying a genetic polymorphism, K55R, associated with elevated levels of sEH, was recognized as a major 2006 intramural research accomplishment by NIH.

Arête plans to focus on diversifying the proprietary family of the inhibitors by increasing specificity, stability and solubility (oral availability) of the compounds before selecting an IND to undergo toxicity testing. If clinical trials proceed as expected, the new drug will take five to six years to undergo the rigorous testing phases required for FDA approval.

Return to Table of Contents

Urology Societies Honor Grantee

By Lillian Gu

NIEHS grantee Shuk-Mei Ho, Ph.D., has won the 2007 Women in Urology Award for Excellence in Urologic Research. The award was jointly presented by the Society of Women in Urology (SWIU) and the Society of Basic Urologic Research at the SWIU's annual meeting in Anaheim, Calif. on May 20. This award recognizes leading female scientists for outstanding contributions to the field of urology.

NIEHS Grantee Shuk-Mei Ho, Ph.D., accepts the 2007 Women in Urology Award at the Society of Basic Urologic Research's annual meeting in May. (Photo courtesy of Shuk-mei Ho)

"Having your work recognized by your scientific peers is the highest honor an investigator can receive," said Ho. "I am proud to accept this award on behalf of all the fabulous women leaders in the field of urology and in science."

Ho was unanimously chosen for this award in recognition of her research in hormonal carcinogenesis. An expert in the field, she has studied the role of hormones and endocrine disruptors in breast, ovarian, endometrial and prostate cancer. In a study published in the June 2006

issue of the journal *Cancer Research*, Ho reported the first evidence of a direct link between developmental exposure to estrogens and prostate cancer in adulthood.

In this study, Ho and her colleagues at the University of Illinois at Chicago found that prenatal exposure to low, environmentally relevant doses of estradiol, the estrogen naturally found in humans, and bisphenol A (BPA), a chemical found in many types of plastic, can make the prostate more susceptible to precancerous lesions in adulthood.

Chair of the Department of Environmental Health at the University of Cincinnati Medical School, Ho has published over 120 scientific articles in peer-reviewed publications. She served as president of the Society of Basic Urology Research (2005-2006) and has served on the NTP Scientific Council for three years. She holds more than $5 million in research grants from the NIEHS, where she has been a grantee for the past three years, National Cancer Institute, Department of Defense, and National Institute of Diabetes and Digestive and Kidney Disorders.

Under an NIEHS grant, Ho is studying how prenatal estrogen exposure can cause permanent changes in gene expression that in turn increase the rate of uterine tumorigenesis in mice.

Ho also holds an Extramural Center Grant from the NIEHS as the director of the University of Cincinnati Center for Environmental Genetics (CEG), which has generated over 400 publications. The CEG promotes integrative research between basic and applied scientists and the translation of that knowledge into clinical practice. It supports both pilot projects and existing research that focus on the interaction between genetics and the environment.

Return to Table of Contents

Science Notebook

UNC Professor Outlines Accomplishments and Challenges of Personalized Medicine

By Eddy Ball

With an impressive grasp of the topic and a healthy infusion of wit and stand-up timing, Howard McLeod, PharmD., kept the audience attentive — and amused — during his June 15 lecture in Rodbell Auditorium. McLeod's talk, titled "Drugs and the Genome: Will it Really Improve Therapy?" was part of the Institute's Frontiers of Environmental Sciences series and was hosted by Senior Scientist Darryl Zeldin, M.D.

McLeod's enthusiasm was obvious as he described how pharmacogenetic research has increased understanding of the drugs warfarin and tamoxifen. (Photo courtesy of Steve McCaw)

McLeod is the Fred N. Eshelman Distinguished Professor and Director of the Institute for Pharmacogenomics and Individualized Therapy at the University of North Carolina at Chapel Hill. He also holds appointments in the Schools of Pharmacy and Medicine, as well as the Lineberger Comprehensive Cancer Center.

McLeod opened his talk by introducing the theme he would develop in the lecture — "trying to make the genome useful to grandma" through research with specific applications in the clinical treatment of illnesses. "We have medicines that benefit many people, but we don't know enough about them to really choose medicines carefully," he explained, "and so understanding mechanisms is really key to achieving this goal of individualized therapy."

According to McLeod, the abundance of FDA-approved drugs for common illnesses, such as colon cancer and hypertension, has made choosing the right medication for an individual patient even more important. Medicine needs to replace the current paradigm of relying on a uniform therapy and dealing afterwards with the patients who do not respond or respond with unacceptable levels of toxicity. Pharmacogenetics, McLeod argued, offers a way to understand an important part of why patients respond differently to the same medication.

To illustrate the potential of integrated pharmacogenetic research, McLeod turned to the case of the very commonly prescribed anti-coagulant drug warfarin. Currently used with over two million patients, this inexpensive drug has a large variability in dosing among patients. Warfarin, he said, is a drug that "costs pennies in terms of the actual pill, but thousands in terms of patient management."

Identifying variability in specific genes that affect detoxification of the drug and the enzyme controlling vitamin K metabolism has allowed clinicians to understand better the influence of genetic factors on the way patients respond to the medication. "This was highlighting to us for one of the first times in clinical medicine how pharmacokinetic variability and pharmacodynamic variability at the gene level come together to explain, in this case, the dose for warfarin for patients," McLeod said.

The results this pharmacogenetic breakthrough led the Food and Drug Administration to consider changing the warfarin package insert to include genetic information as part of the risk identification for warfarin. Physicians can now take advantage of a web site supported by the Barnes-Jewish Hospital at Washington University Medical Center, the NIH and other donors for guidance in determining the best dose for their patients.

Along with its effects on safe and effective treatment, individualized medicine also has financial implications — and physicians, insurance companies and malpractice attorneys are now paying attention to them. For example, physicians are painfully aware of the added burden of treating patients who fail to respond to uniform therapies, and payers are looking to genetics as a way of justifying more expensive treatments for breast cancer patients as an alternative to the drug tamoxifen.

McLeod emphasized that there are still many challenges and questions to be answered, and much more discovery work needs to be done to find the right biomarkers. Physician attitudes need to change, and patients need to demand more real personalized medicine. Still, important advances, especially from large clinical trials now underway, are taking place to give researchers improved access to the robust data sets they need.

"Genetics will be a contributor to better medical decision making," McLeod concluded. "It will not be the [only] source of better decision making.…[but] we're now actually able to go and do intervention."

Return to Table of Contents

Among the scientists who turned out for McLeod's lecture was Epidemiologist Stephanie London, M.D. (Photo courtesy of Steve McCaw)

Host Darryl Zeldin monitored questions from the audience following the lecture. (Photo courtesy of Steve McCaw)

Princeton Scholar Explores Use of Science in Policy Debates

By Lillian Gu

On June 8, the NIEHS Frontiers of Environmental Sciences Lecture Series featured a talk on science policy by guest lecturer David Goldston in Rodbell Auditorium. The former Chief of Staff of the U.S. House of Representatives Committee on Science, Goldston is currently a Practitioner-in-Residence at Princeton University's Woodrow Wilson School of Public and International Affairs. In his talk titled "Loving Science to Death?: How and Why Politicians Use and Misuse Science in Policy Debates," Goldston explored the role of science in environmental policy debate, emphasizing to the near-capacity audience the importance of scientists in the political arena.

The talk was unique in that it was the first in the Frontiers of Environmental Sciences Lecture Series to focus on policy rather than on basic science. In addition, the lecture was an interagency event hosted by Jack Fowle, Ph.D., acting director of the Neurotoxicology Division of the Environmental Protection Agency's National Health and Environmental Effects Research Laboratory.

In his talk, Goldston discussed the tendency nowadays for every policy issue to be framed as a science question and the reasons behind this trend. He pointed out "the general high esteem …that science is held in" encourages both ends of the political spectrum to use science to bolster their respective policies. Goldston also cited the partisanship of political leaders. "This highly divided political elite has to figure out a way to engage the public, a public that is not as polarized," explained Goldston, "And one way to do that is to use science."

While this attention to science may be a blessing, Goldston warned that it is also a curse, a trend that may be harmful to both science and policy-making in the long run. "Most issues… ultimately are questions of value and policy," Goldston asserted. "Science becomes a way to avoid discussing the issues that the political system and the democracy really need to address."

Using deliberations on ozone regulations in 1977 as an example, Goldston demonstrated the difference between a policy debate and a science debate. The science question was, "Is there a threshold level below which ozone is safe?" Since the general scientific consensus was that ozone caused aggravated respiratory ailments at any exposure, the issue emerged as a policy question: "How many hospital admissions are acceptable public policy?" In the end, discussion of this tricky question was avoided and, instead, both sides attacked the underlying science. Although Congress passed the regulations, Goldston pointed out the drawbacks of such a process.

To avoid similar situations, Goldston suggested three fundamental questions to ask when science and policy intersect:

- To what extent does the policy dispute revolve around a science question?
- How much consensus is there on that science question?
- What policy options does the science leave on the table?

Goldston emphasized that presenting the existing levels of uncertainty is important to maintain the credibility of science in the long run. In addition, he recommended that scientists do their "homework" before entering policy discourse. Lastly, Goldston emphasized the importance of scientists in the policy world, especially at a time when science is so heavily emphasized in policy-making.

Former Chief of Staff of the U.S. House of Representatives Committee on Science David Goldston (Photo courtesy of Steve McCaw)

John Schelp, Office of Policy, Planning and Evaluation, listens attentively. (Photo courtesy of Steve McCaw)

The audience present came from various departments, including Richard Maclehose, Ph.D., center, Biostatistics Branch, and Shannon Laughlin, Ph.D., right, Office of Intramural Research. (Photo courtesy of Steve McCaw)

Deputy Scientific Director Bill Schrader commented on the role of science in policy making. (Photo courtesy of Steve McCaw)

Jack Fowle of EPA hosted the interagency event. (Photo courtesy of Steve McCaw)

Return to Table of Contents

PI Outlines Upcoming Developments in Nicotinic Receptor Research

By Eddy Ball

Neurobiologist Jerrel Yakel, Ph.D., used the occasion of his upcoming Board of Scientific Counselors' review as the platform for a lecture on June 6 in Rall F-193. Speaking on "Nicotinic Receptor Channel: Structure, Function and Possible Roles in Neurological Disorders and Disease," Yakel, who is a senior investigator in the Laboratory of Neurobiology at NIEHS, surveyed his recent work in the field and described the direction his group's work will take in the next year and beyond.

Using electrophysiology, iontophoresis and fluorescence imaging techniques, Yakel's lab has studied activation of neuronal nicotinic acetylcholine receptors (nAChRs) in the hippocampal and cortical sections of the brains of mammals and the receptors' induction of calcium (Ca^{2+}) signals. He and his colleagues have mimicked synapses in brain slices to evaluate rates of activation, desensitization and Ca^{2+} permeability of receptors.

Situated in the soma and, to a lesser extent, in the dendrites of neurons, nAChRs are ligand-gated ion-channel receptors that mediate fast excitory synaptic transmission in the central and peripheral nervous system. Receptor regulation of calcium has been linked to a variety of functions in the brain related to synaptic transmission. How effectively these receptors mediate rapid electrical impulses in the nervous system can impact the development of neurons, learning and memory formation, and reward mechanisms, such as pleasure and satiation.

IRTA Fellow Daniel Brown, Ph.D., left, of the LN Polypeptide Hormone Group stayed after the lecture to ask Yakel more questions about his work. (Photo courtesy of Steve McCaw)

Along with their role in helping to maintain nicotine addiction through reward reinforcement, hence the designation "nicotinic," these receptors are a potential therapeutic target in several disease conditions of wide concern to the medical and research community:

- Alzheimer's Disease — dementia may be associated with deficits in cholinergic synaptic transmission
- Parkinson's Disease — epidemiological and recent *in vivo* animal research suggest nicotine may have a protective effect
- Epilepsy and neuromuscular diseases — the excitotoxic effects of a rapid influx of calcium into neuronal cells in the brain may exacerbate the conditions
- Schizophrenia — the high incidence of heavy smoking among patients could be a form of self-medication
- Pain — manipulation of nAChRs may enhance the effects of analgesic compounds that work through these receptors

Thus far, scientists have identified 11 subunits of nAChRs that affect synaptic transmission in different sections of the brain. Receptor subunits are designated by combinations of a Greek alphabetical character and an Arabic numeral, such as α7 and β4 (see graphic on "Distribution and possible roles of nAChRs").

"nAChRs," Yakel wrote in his most recent study, "have the capacity to elicit changes in cytoplasmic calcium ($[Ca^{2+}]_i$) levels, which has implications for regulating various signal transduction cascades, synaptic plasticity, and memory processes." Consequently, understanding the mechanisms by which the subunits of nAChRs influence calcium can help researchers identify their effects on epigenetic alterations related to the development of neurodegenerative disorders.

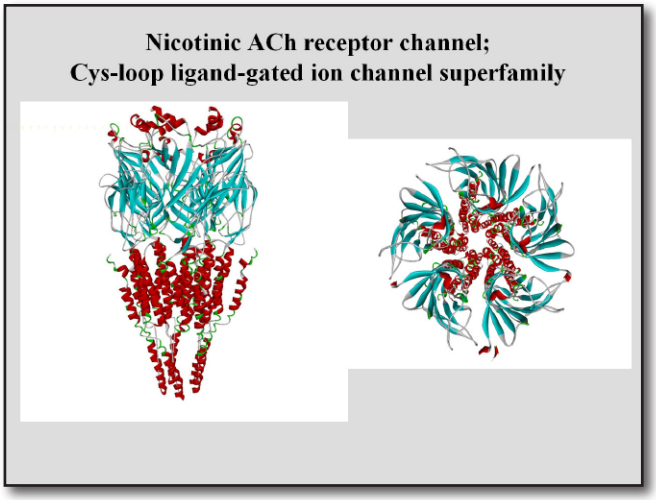
Yakel also gave the audience a preview of his most recent study, a collaboration with former LN Research Fellow Dmitriy Fayuk, Ph.D., that is still in press. This research reports for the first time the spatial and temporal properties of the $[Ca^{2+}]_i$ signals and currents stimulated by the rapid activation of α7-containing nAChRs in the dendrites of interneurons in hippocampal slices and cultured hippocampal neurons. To evaluate properties of these signals and currents, the researchers measured signaling distance in microns and duration in milliseconds.

Looking Ahead

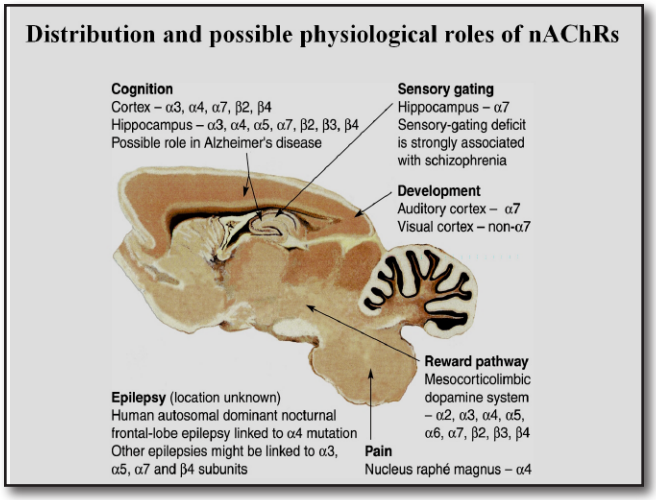
Future directions for Yakel and his colleagues in the LN Ion Channel Physiology Group involve exploring receptor activation in other areas of the brain, including the amygdala, the region suspected of involvement in fear and aversively motivated memory, and the basal ganglia, with its implications in dopamine synthesis and Parkinson's Disease. When he takes the podium in his presentation to the Board of Scientific Counselors reviewing the work in his lab, Yakel will offer three future directions for their consideration:

- Tracing cholinergic synapse development (co-cultures) and the regulation of synaptic signaling
- Tagging receptors with green fluorescent proteins and quantum dots, a cutting-edge nanotechnology used in pharmacokinetics studies, to evaluate mobility in membranes and cycling patterns
- Delineating the role of nAChRs in inflammation, glial cell damage and phosphorylation of a protein family known as MARCKS (myristoylated alanine-rich C-kinase substrate)

Biologist Joel Abramowitz, Ph.D., center, representing the Office of Scientific Director, and Laboratory of Pharmacology and Chemistry Supervisory Pharmacologist John Hong, Ph.D., right, talked with Yakel about his presentation. (Photo courtesy of Steve McCaw)



Activation of α7-containing nAChRs stimulates signals in the form of ions with electrical charges, such as sodium ions (Na^+) or calcium ions (Ca^{2+}), that send messages from the brain throughout the nervous system. (Graphic model courtesy of Jerrel Yakel and Rachelle Bienstock)



Yakel's group is working to establish connections between specific receptor subunits, such as α7, with brain functions and neurological disorders. (Graphic courtesy of Jerrel Yakel)

As impressive as the advances in this research have been, Yakel readily admits that there are many questions still to be answered. "[For example,] we still don't exactly know the synaptic aspect of these receptors," he conceded. "We're trying very hard to figure it out and garner the tools to do that."

Return to Table of Contents

Baylor Ethicist Addresses Confidentiality of Genetic Data

By Lillian Gu

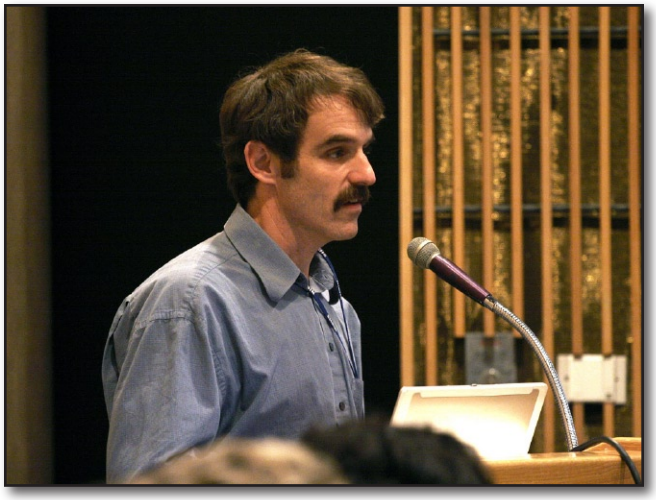
In an event hosted by NIEHS bioethicist David Resnik, J.D., Ph.D., on June 15, Amy McGuire, J.D., Ph.D., from the Baylor College of Medicine delivered an intriguing talk titled "The Confidentiality of Human Genetic Research." McGuire, a bioethicist, is an assistant professor in the Baylor Center for Medical Ethics and Health Policy with research interests in informed consent and genetic confidentiality.

McGuire explained how the Human Genome Project, the International HapMap Project and other large-scale genomic sequencing initiatives have transformed the field of genetics. To illustrate this point, she said that in May 2007, 53 years after James Watson and Francis Crick made their historic discovery of DNA's helical structure, Watson was presented with his own personal genome on two DVDs during a press conference in Houston.

As DNA sequencing has become faster and less expensive, a data sharing dilemma has emerged pitting utility against privacy. "We're always making tradeoffs between advancing science, promoting the utility of the data and promoting individual privacy," stated McGuire, "and I am most interested in these tradeoffs."

The current trend is to rapidly release generated data, McGuire explained, based on the assumption that privacy is being protected. Because name and other personal information are replaced by a numerical code when a sample passes hands from the clinical researcher and the DNA sequencer, the coded data is considered "de-identified."

McGuire was bioethicist for the team that sequenced Watson's genome. (Photo courtesy of Steve McCaw)



NIEHS Bioethicist David Resnik hosted the talk. (Photo courtesy of Steve McCaw)

Currently, McGuire said, there is limited protection of genetic information in the United States. The Health Insurance Portability and Accountability Act protects "identifiable protected health information." The Common Rule requires informed consent and approval from the Institutional Review Board (IRB) when such information is obtained in human research, but coded genomic data, like blood and tissue samples, are not considered identifiable.

However, critics argue that DNA in itself is a unique identifier, so "de-identified" data is not truly de-identified. McGuire cited a paper by Lin et al. in *Science*, which states, "Specifying DNA sequence at only 30 to 80 statistically independent SNP [single nucleotide polymorphism] positions will uniquely define a single person." In the case of individuals with rare alleles or individuals for whom additional family information is available, only a few SNP positions are necessary — making the distinction between private and identifiable problematic.

A National Human Genome Research Institute workshop last year established possible methods of re-identifying individuals through their DNA, which include matching to reference samples, linking information from various databases and profiling with probabilistic data.

In reassessing the privacy-utility tradeoff, there has recently been a policy shift towards privacy, leading to a proliferation of databases with access restricted in the form of passwords and even proposals to require IRB approval. While restrictions such as these increase privacy, such protective measures are expensive and may severely limit accessibility. Other efforts to protect privacy include fragmenting or statistically degrading the data.

In a focus group with research participants in an epilepsy study, McGuire found that interest in data release was high, but most participants felt the decision should be left to them, rather than to the federal government or an institution.

McGuire agreed. "From the perspective of personal autonomy and dignity, people have a right to decide with whom they want to share their personal information."

"It's very important that research participants have trust in the research enterprise," she added. "Even if they are not harmed by the release of their information,… they still may lose trust if they find out that a lot of people who they might not want to have access to their information are getting access to their information. Without research participants, we don't have research."

Return to Table of Contents

Extramural Update

Centers for Neurodegeneration Science (CNS)

The NIEHS Division of Extramural Research and Training, in conjunction with the National Institute on Aging, recently announced revised dates for the new Centers for Neurodegeneration Science (CNS) grants to conduct integrated programs of research. These centers will support human studies in combination with basic mechanistic research in relevant model systems to understand how environmental factors contribute to the etiology, progression, phenotypic expression, treatment and/or prevention of neurodegenerative diseases.

Neurodegenerative diseases are the result of deterioration of cells of the brain or spinal cord, the continued loss of which leads to progressive impairment. Millions of people worldwide are afflicted with neurodegenerative disorders, and therapies provide limited symptomatic relief, but do not halt the progression of the disease. Studies of mono- and di-zygotic twin pairs demonstrate the importance of non-genetic factors in disease etiology.

The goals of the CNS program are to provide a mechanistic understanding of the role(s) of environmental factors in human neurodegenerative disease; identify and pursue opportunities for translation of this knowledge to the intervention and/or prevention of neurodegenerative disease; establish an interdisciplinary framework that fosters integrative research by neurodegenerative disease researchers and environmental health scientists; support the development of novel and complementary lines of investigation by non-CNS investigators; and promote meaningful collaborations and sharing of data and resources with other Centers.

Each CNS must be focused around a central theme regarding the role of environmental factors in the etiology, phenotypic expression, progression, intervention and/or prevention of a complex human neurodegenerative disease and be comprised of three or more projects which embody a full range of research approaches from basic research to human studies.

The revised dates are as follows:

- Letters of Intent Receipt Date: August 24, 2007
- Application Receipt Date: September 24, 2007
- Peer Review Date(s): January-February 2008
- Council Review Dates: May 2008
- Earliest Anticipated Start Date(s): July 1, 2008
- Expiration Date: September 25, 2007

Inquiries should be directed to Program Administrator Cindy Lawler, Ph.D., by e-mail or phone at (919) 316-4671.

Return to Table of Contents

Extramural Papers of the Month

By Jerry Phelps

S-nitrosothiols: Possibilities in Fighting Asthma and Heart Disease

Jonathan Stamler and colleagues at Duke University and the Howard Hughes Medical Institute report in the May 4th issue of *Cell* new findings suggesting the endogenous compound S-nitrosothiol may have clinical implications for a variety of diseases including asthma and heart failure. They found that S-nitrosothiol, a specialized form of nitric oxide, inhibits a key regulatory system that ordinarily shuts off receptors once they have been stimulated.

The G-protein coupled receptors represent the largest known family of cell-surface receptors and are involved in many aspects of mammalian physiology including processes as diverse as responses to odorants, light, and pain. About half of all drugs on the market today target the G-protein coupled receptors. Many of these drugs lose their effectiveness over time because the receptors they target are recycled into the cell and are turned off.

In a series of experiments in laboratory animals and cell culture systems, the researchers found that a lack of nitric oxide led to a decrease in the number of beta adrenergic receptors on the surface of cells. Administration of S-nitrosothiols to mice prevented the receptors from being turned off. If these findings are confirmed in humans, they may lead to the development of new non-sensitizing therapeutic agents for many conditions such as heart disease, asthma, high blood pressure, chronic pain, diabetes and others.

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

Return to Table of Contents

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

Astrocytes carrying a version of the mutant protein that causes amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, are responsible for the death of motor neurons, reported NIEHS grantee Serge Przedborski in the May 2007 issue of *Nature Neuroscience*.

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

The researchers also reported that the astrocytes expressing mutant SOD1 killed only spinal motor neurons that degenerate in ALS and not other types of neurons. They show that cell death was due to a soluble toxic factor released by the astrocytes. These findings suggest that stem cell therapy focused on replacing damaged neurons may not be feasible in ALS because mutant astrocytes would most likely kill the replacement neurons. If the toxic factor can be identified in future studies, this finding may offer novel strategies for therapy.

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

Return to Table of Contents

Green Tea and Skin Cancer

A study funded by NIEHS and the National Cancer Institute reported that drinking green tea can reverse the effects of sun damage to the skin and prevent skin cancer. The study found that green tea prevents UV radiation-induced suppression of the immune system, which has been considered a risk factor for skin cancer.

Green tea has been shown to be rich in antioxidant and anti-inflammatory compounds known as polyphenols and epigallocatechins, which are known to have anti-carcinogenic qualities. In this study, the researchers found that drinking green tea may also help doctors treat internal cancers and heal the pre-cancerous rough, scaly keratosis that some people get from prolonged, chronic exposure to the sun.

The study found that in a mice model, green tea polyphenols administered in drinking water or the application of epigallocatechin-3-gallate to the skin prevented skin tumors through a variety of mechanisms including the induction of interleukin 12, interleukin 12-dependent DNA repair following nucleotide excision repair, inhibition of ultraviolet radiation-induced immunosuppression and angiogenic factors, and stimulation of cytotoxic T-cells in the tumor microenvironment.

The study still needs independent confirmation, but it offers hope for a new and significant therapy for the prevention of skin cancer and a new treatment option for patients suffering from skin cancer.

Citation: Katiyar S, Elmets CA, Katiyar SK. 2007. Green tea and skin cancer: photoimmunology, angiogenesis and DNA repair. J Nutr Biochem 18(5):287-296.

Return to Table of Contents

Mercury Content Reduced in Daphnia Fed High Quality Algae

New research by NIEHS-funded scientists at Dartmouth College finds that organisms fed nutritious, high-quality food end up with much lower concentrations of toxic methylmercury in their tissues. The result suggests ways in which methylmercury, a neurotoxin that can accumulate to hazardous levels, can be slowed in its passage up the food chain in fish and ultimately to humans.

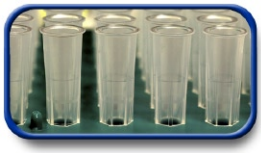
The investigators studied the water flea *Daphnia pulex*, a species of plankton that is one of the chief food sources for freshwater fish. The team measured, over five days, the growth of two groups of juvenile *Daphnia*. Both groups were fed the same amount of algae contaminated with trace amounts of methylmercury; however, one group's algae was of greater nutritional value.

The *Daphnia* that received the nutritious, phosphorous-rich algae grew 3.5 times faster than the other group. They also ended up with one-third the concentration of the toxin in their tissues because the toxin was diluted.

Daphnia and other plankton are a major source of methylmercury for lake fish. The research suggests that when water fleas and other organisms grow rapidly by feeding on high quality food, the rate at which methylmercury is accumulated and transferred through the food chain may decrease.

Citation: Karimi R, Chen CY, Pickhardt PC, Fisher NS, Folt CL. 2007. Stoichiometric controls of mercury dilution by growth. Proc Natl Acad Sci U S A. 104(18):7477-7482.

Return to Table of Contents



Intramural Papers of the Month

By Eddy Ball

Enzyme Linked to Oxidative Damage in Huntington's Disease

A team of researchers from NIEHS, Mayo Clinic and Foundation, and the University of Oslo have demonstrated *in vivo* the role of a base excision repair (BER) enzyme, 7,8-dihydro-8-oxoguanine-DNA glycosylase (OGG1), in triggering the age-dependent somatic mutation associated with Huntington's disease (HD) that leads to progressive toxicity in somatic cells. In an NIH Intramural Program-supported study published in the May 24 issue of *Nature*, the scientists described a "toxic oxidation" model in which the enzyme initiates a process that leads to increasing frequency of an error in the BER of single-strand breaks (SSB) in DNA known as CAG trinucleotide expansion.

The team used transgenic male mice and female partners lacking one of the glycosylases and their litters, which had been bred until they were homozygous knockouts, to generate *in vivo* data for the study. They investigated the correlation of CAG expansion with DNA oxidation, normal repair of SSB, and the presence or absence of OGG1. They also performed parallel experiments *in vitro* with human HD fibroblasts and lymphoblasts.

The researchers discovered an "unexpected specificity for OGG1" in triggering CAG expansion in HD *in vivo*. That insight into the mechanism, they concluded, may have "general relevance to late onset neurodegeneration" in other conditions as well.

Citation: Kovtun IV, Liu Y, Bjoras M, Klungland A, Wilson SH, McMurray CT. 2007. OGG1 initiates age-dependent CAG trinucleotide expansion in somatic cells. Nature 447(7143):447-452. doi:10.1038/nature05720.

Return to Table of Contents

Carbonated Beverages and Risk for Chronic Kidney Disease

In an Intramural Research Program-funded study published in the July issue of *Epidemiology*, NIEHS Epidemiology Branch investigators reported a two-fold risk of kidney disease among subjects who reported drinking two or more glasses of cola a day. The scientists speculated that the use of phosphoric acid in the production of cola beverages may account for the significant association, which was not found in non-cola carbonated beverages.

The researchers collected data through telephone interviews with subjects or proxy respondents for 465 case subjects who had been newly diagnosed with kidney disease at four North Carolina hospitals between September 1980 and August 1982. The investigators also interviewed 467 NC residents without a history of kidney disease. The researchers found that the more colas a person reported drinking, the greater the risk of kidney disease.

Although the study had several limitations, including reliance on self-reporting, the authors were careful to control for confounding factors. In light of the rising incidence and costs of chronic kidney disease, which now affects over 20 million adults in the U.S., the authors concluded, "Our preliminary result of an association… deserves to be explored in more detailed studies."

Citation: Saldana TM, Basso O, Darden R, Sandler DP. 2007. Carbonated Beverages and Chronic Kidney Disease. Epidemiology 18(4):501-506.

Return to Table of Contents

RNA Direct Transfer of Genetic Information

A team of researchers in the NIEHS Laboratory of Molecular Genetics has published data providing evidence demonstrating that RNA can directly serve as a template in the repair of chromosomal DNA lesions in the yeast *Saccharomyces cerevisiae*. Their intramural research funded study, which appeared in the May 17 issue of *Nature*, significantly expanded previous research findings that had demonstrated mediation of recombination by RNA, but only indirectly through a complementary DNA intermediate.

The scientists induced DNA damage in the form of a unique double-strand break (DSB), which was then targeted with a type of nucleic acid segment, known as a single-strand oligonucleotide, to repair the break. These experiments were performed in a carefully controlled environment to exclude the possibility that DNA contamination might be responsible for the transfer of genetic information. The team also studied DNA synthesis reactions with DNA polymerase enzymes from *S. cerevisiae* that are candidates in the DNA repair process.

The researchers described their findings as generally relevant to DNA repair since much of the genome of any organism is involved in synthesizing RNA, which could be used in a reverse manner to repair corresponding regions of damaged chromosomes. The study also demonstrates how RNA that may be present in the mammalian mitochondrial DNA genome could be copied during replication. Suggesting translational applications of the research, the team concluded, "The ability of RNA to transfer genetic information to homologous chromosomal DNA could lead to new directions in gene targeting given that RNA can be amplified at will within cells."

Citation: Storici F, Bebenek K, Kunkel TA, Gordenin DA, Resnick MA. 2007. RNA-templated DNA repair. Nature 447(7142):338-341. doi:10.1038/nature05720.

NOTE: This paper is featured in this month's ***Nature* top ten** — a list of the ten articles most frequently downloaded from the *Nature* website as PDFs each preceding month. The full list for this month is at http://www.nature.com/nature/topten/index.html.

Return to Table of Contents

Mechanisms of Ozone-Induced Lung Injury in Mice

In the April issue of the *American Journal of Respiratory and Critical Care Medicine*, an NIEHS-funded team of scientists reported new discoveries about signal transduction pathways of tumor necrosis factor receptor (TNF-R)-mediated lung injury induced by ozone (O_3), a principal oxidant in air pollution. Based on their previous findings from a genetic linkage analysis in which TNF has been found as a candidate susceptibility gene for pulmonary inflammation by O_3, the investigators studied the roles of two pathways that serve as downstream effectors of TNF in lung injury - nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase/activator protein 1(MAPK/AP-1).

To elucidate the molecular mechanisms underlying TNF-mediated lung injury induced by O_3, the researchers exposed three knock-out strains of mice and their respective wild-type mice to concentrations of O_3 proportionate to exposure levels experienced by humans. Animal lungs and lung tissue were then examined for differences in histopathology, cellular inflammation and hyperpermeability, and molecular changes including DNA binding activity and mRNA abundance. The researchers were able to pinpoint which genetic profiles, and consequently which signal transduction pathways, influenced the animals' reactions to O_3 exposure.

This study demonstrated that NF-κB and MAPK/AP-1 played important roles in O_3-induced lung inflammation and injury mediated through TNF-R. The authors concluded that "the current study provided details of molecular events underlying pulmonary O_3 toxicity," a potentially important advance in discovering therapeutic targets for sufferers of allergy and asthma in association with environmental O_3 exposure.

Citation: Cho HY, Morgan DL, Bauer AK, Kleeberger SR. 2007. Signal transduction pathways of tumor necrosis factor--mediated lung injury induced by ozone in mice. Am J Respir Crit Care Med 175(8):829-839.

Return to Table of Contents

Inside the Institute

Institute Welcomes 2007 Summers of Discovery Interns

By Lillian Gu

Young aspiring scientists from academic institutions across the nation gathered on the NIEHS Patio for the 2007 Summers of Discovery Annual Picnic on June 13. For 8-12 weeks during May through September, each of these 75 interns will work closely with an NIEHS mentor to gain hands-on research experience in disciplines ranging from epidemiology and computer modeling to signal transduction and cancer biology.

Over three times as many young scholars applied to the program this year than were accepted, and those who made it appreciate the opportunity they have at the Institute. University of Wisconsin undergraduate Ben Dickey remarked, "Everyone at the lab has been incredibly welcoming. I'm honored to be here." Dickey is working with Jonathan Freedman, Ph.D., Laboratory of Molecular Toxicology, in the Comparative Genomics Group.

During a brown bag networking lunch with fellow interns, Earlham College undergraduate Katie Putney said, "I've had a lot of fun. I really enjoy learning about the research the lab is working on."

Intern Katie Putney enjoys a brown bag lunch during orientation. Putney is working with David Armstrong, Ph.D., in the Laboratory of Neurobiology. (Photo courtesy of Steve McCaw)

2007 Summers of Discovery Weekly Seminar Series

Most seminars take place on Wednesdays at 11:00 a.m. in Rodbell Auditorium Conference Room 101B.

- **May 23.** "Xenobiotic Transport, ATP-Driven Transporters and the Blood-Brain Barrier" by David Miller, Ph.D., Intracellular Regulation, Laboratory of Pharmacology & Chemistry
- **May 30.** "Relationships Between DNA Replication (In)Fidelity and Human Diseases" by Tom Kunkel, Ph.D., Laboratory of Structural Biology
- **June 20.** "Using Microarrays to Look for Biomarkers of Injury or Diseases in your RNA" by Richard Paules, Ph.D., NIEHS Microarray Group; Laboratory of Molecular Toxicology
- **June 27.** "Allergic Sensitization through the Airway" by Donald Cook, Ph.D., Laboratory of Respiratory Biology
- **July 11.** "Regulating Gene Expression by Holding Back Transcription Elongation" by Karen Adelman, Ph.D., Laboratory of Molecular Carcinogenesis
- **July 18.** "The Molecular Biology of Bugs, Worms, Fish and Mice" by Jonathan Freedman, Ph.D., Laboratory of Molecular Toxicology.
- **August 1.** "Respiratory Virus Infections and Immune Respones" by Farhad Imani, Ph.D., Laboratory of Respiratory Biology.

In addition to the research mentoring experience, interns will also take tours of the Institute's library and special workshops on poster preparation and presentation skills, laboratory safety, and animal research. This year's program features some of the Institute's leading researchers in weekly seminars. (See side panel for a schedule of the seminars.)

2007 Summers of Discovery Interns and Mentors pose for the Annual Photo. Writer/photographer Lillian Gu sits to the right of Charle League, seated center.(Photo courtesy of Steve McCaw)

Because the participants and their mentors decide on their own schedule, the interns' arrivals have been staggered and program coordinator Charle League has had the opportunity to welcome many of the participants individually. "We have a promising group this year," commented League, "and an excellent set of speakers lined up."

While 39 of participants are college undergraduate students, the program also has 14 high school students, 14 graduate students, 7 college faculty and one middle school teacher. There is an equal division of out-of-state and North Carolina residents.

Participants will present their research at the annual poster session on July 25 and attend the Awards Ceremony on July 27.

Established by the Division of Intramural Research in 1989, Summers of Discovery is a full-time research program open to high school, undergraduate and graduate students interested in pursuing careers in the biological sciences. The program directly promotes Goal VI of the 2006-2011 NIEHS Strategic Plan to "recruit and train the next generation of environmental health scientists" with its unique opportunity to work with leading research scientists at the Institute.

Scenes from the 2007 Summers of Discovery Annual Picnic

Program coordinator Charle League passes around permanent markers for students and mentors to write name tags at the 2007 Summers of Discovery Annual Picnic (Photo courtesy of Lillian Gu)

Summer intern Laurine Tiema poses with her mentor, Ron Cannon, Ph.D., Laboratory of Molecular Toxicology. (Photo courtesy of Steve McCaw)

Chris Geyer, Ph.D., Laboratory of Reproductive and Developmental Toxicology, listens as summer interns share their experience. (Photo courtesy of Steve McCaw)

Darryl Zeldin, M.D., Laboratory of Respiratory Biology, interacts with summer interns after lunch. (Photo courtesy of Steve McCaw)

Gary Burke, left, Laboratory of Pharmacology and Chemistry, and Kevin Gerrish, Ph.D., Laboratory of Molecular Toxicology, enjoy lunch together. (Photo courtesy of Steve McCaw)

Gary Bird, Ph.D., Laboratory of Signal Transduction, interacts with summer interns. (Photo courtesy of Steve McCaw)

Researchers from the Laboratory of Respiratory Biology mingle with summer interns. (Photo courtesy of Lillian Gu)

[Return to Table of Contents](#)

GLBT Pride Month at NIEHS

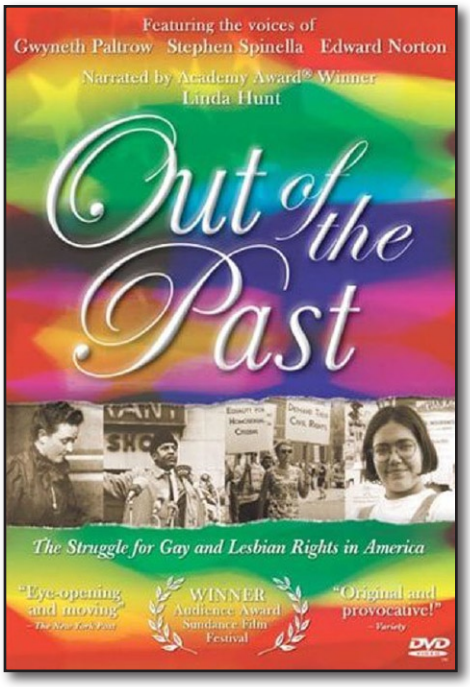
By Eddy Ball

Columbia University Psychologist Ilan Meyer (Photo courtesy Paula Juras)

Two events in the NIEHS 11th Annual Noon-in-June series sponsored by the NIEHS Diversity Council highlighted the orientation-specific challenges and accomplishments of gay, lesbian, bisexual and transgender (GLBT) individuals. On June 5, employees gathered in B200 to watch the videocast of a lecture on "The Impact of Prejudice on the Mental Health of Lesbians, Gay Men and Bisexuals" by Ilan Meyer, Ph.D. Two weeks later, on June 19 in the Executive Conference Room, the NIEHS Diversity Council aired the gay pride documentary film "Out of the Past."

Meyer's lecture was based on his extensive work on gender-specific stress at the Mailman School of Public Health at Columbia University, where he is associate professor and deputy chair of Master of Public Health Programs, Sociomedical Sciences. The lecture outlined a conceptual framework for understanding the higher prevalence of mental health disorders observed in GLBT individuals as compared to heterosexuals.

According to Meyer, the added stress of stigma, prejudice, and discrimination creates a hostile and stressful social environment, compounding the normal stresses of life. The additional stresses, which he describes as "minority stress," lead to a higher rate of mental health problems among minorities, especially those who belong to two or more minority groups.



His model described stress processes, including the experience of prejudice events, expectations of rejection, hiding and concealing, internalized homophobia and ameliorative coping processes. The added burden of minority stress can have a negative impact on the work performance, social interactions and personal relationships of individuals affected.

The companion to Meyer's lecture, the film "Out of the Past: The Struggle for Gay and Lesbian Rights in America" (1998), featured the voices of narrator Linda Hunt, Gwyneth Paltrow and Edward Norton and was directed by Jeff Dupre. Originally shown on public television, the film is told through the eyes of Kelli Peterson, a 17-year-old high school student and GLBT activist in Salt Lake City, Utah.

The film explores Peterson's experiences forming a Gay Straight Alliance in her public school in an attempt to bring about open discussion on the subject of sexuality. "Out of the Past" also intersperses profiles of past movements and their activists into the narrative, providing insights into gay and lesbian struggles throughout American history.

The film develops a central theme about the link between self-respect and history, introduced early in the narrative by Yale University historian George Chauncey. "If we don't find ourselves in the past," he observed, "it's like we don't exist in the present."

Return to Table of Contents

Future Health Care Professionals Visit NIEHS

By Eddy Ball

Fifty participants in the 2007 Science Enrichment Preparation Program ended their day at NIEHS on June 8 by attending a series of short lectures in Rodbell Auditorium. The young people are students who have declared an interest in careers in medical science and are attending institutions in the University of North Carolina (UNC) system and several private colleges in North Carolina.

The program was coordinated by Marian Johnson-Thompson, Ph.D., director of Education and Research Development at NIEHS and utilized the role-modeling talents of several scientists at the Institute, who, like the participants, are members of historically underrepresented groups. The program is one of several Institute initiatives that endeavor to nurture talented young scientists from minority groups and increase the diversity of professionals in the scientific and health care communities.

Following welcome remarks by Johnson-Thompson, the afternoon program began with viewing a UNC-TV "North Carolina Now" segment on the Sister Study. The program was titled "A Study of the Environmental and Genetic Risk Factors for Breast Cancer" and featured an interview with several participants and Principal Investigator Dale Sandler, Ph.D., of the NIEHS Epidemiology Branch.

Along with information about Yakel's research, the students were interested in how much research scientists make at NIH. (Photo courtesy of Steve McCaw).

An Educator's Best Reward

Each year, Johnson-Thompson touches the lives of hundreds of young people all over the country — often without ever learning how much impact she had on their lives. Recently, she learned that three young scientists she mentored, high school students in St. Petersburg, Fla. working on a greenhouse gases project, were among the finalists in the 2007 Internet Science and Technology Fair (ISTF). Johnson-Thompson has worked with students competing in the ISTF for several years, but this is the first group to reach the finalist stage.

The team members ended their message to Johnson-Thompson with the words that mean so much to a teacher. "We just want to let you know that we thank you so much for the helps and contribution you have made throughout our freshman year," wrote Hang, Victoria and Jordan. "Well, we're almost sophomores and we hope that we will have you as our mentor in the future."

Johnson-Thompson also got some very positive feedback on the presentation by Dario Ramirez during the 2007 Science Enrichment Preparation Program. Ramirez received an e-mail from one of the students in attendance, a rising senior majoring in Biochemistry at East Carolina University in Greenville, North Carolina. The young chemist, who hopes to become a pharmacologist or a research pharmacist working in drug development, was profoundly influenced by the presentation on oxidative stress.

"During the presentation I learned a lot about free radicals, and how unstable and reactive they are in macromolecules found in the body," the young man wrote. "I also gained a lot of interest in your research.… Your background story… made me more eager to work with you and be mentored by someone with that much knowledge, experience and similar career goals."

The rest of the program featured short lectures on their research by some of the Institute's leading young and mid-career scientists:

- Senior Scientist Jerrel Yakel, Ph.D., described his research into "How the Brain Works: Understanding Neuronal Signaling." Yakel is head of the Ion Channel Physiology Group in the Laboratory of Neurobiology.

- Staff Scientist Pierre Bushel, Ph.D., introduced the students to "Bioinformatics for a Better Understanding of Biology." Bushel's work merges biology and informatics in the Institute's Biostatistics Branch.

- Principal Investigator-in-Training Dario Ramirez, Ph.D., explored the topic of "Oxidative Stress and Inflammation: Biological Response to Environmental and Metabolic Stressors." Ramirez is a member of the Free Radical Metabolites Branch in the Laboratory of Pharmacology and Chemistry.

The audience laughed as Bushel described his work as "triple-nerd science," but they were certainly impressed by the salaries Ph.D. bioinformatics specialists can demand. (Photo courtesy of Steve McCaw)

The students visited the NIEHS campus through a cooperative agreement with the North Carolina Health Careers Access Program (NC-HCAP) administered through UNC-Chapel Hill. According to the organization's mission statement, "NC-HCAP envisions a society with equitable access to culturally competent health care across all racial and ethnic groups irrespective of geographic location (urban or rural) or socioeconomic status - in short, a society where no health disparities exist."

Return to Table of Contents

The young people were intrigued by Ramirez' research and inspired by the story of his childhood and youth in Argentina. (Photo courtesy of Steve McCaw)

Johnson-Thompson was surprised at the students' career choices, all of which involved direct patient care. "This is the first group I've ever had that didn't have at least one researcher in it," she said. (Photo courtesy of Steve McCaw)

Tree Planted for Kari at NIEHS Memorial Garden

By Eddy Ball

A robust Frank Kari before his illness. (Photo courtesy of Steve McCaw)

On June 6, friends of Toxicologist Frank Kari filled Rodbell C to remember their colleague during a special slide show presentation narrated by Research Physiologist Jef French, Ph.D., and organized with the help of Biologist Betsy Kennington. Afterwards, most of those in attendance took part in the planting of Kari's tree, a red bud donated by his colleagues in the Blackshear and Petrovich labs.

Return to Table of Contents

Many of those in attendance placed shovels full of earth around the red bud sapling. French, with shovel in hand, took his turn as Toxicologist James Huff, Ph.D., looked on. (Photo by Eddy Ball)

In this 2005 photo, Kari, right, is shown with two of the young scientists he mentored, Martyn Darby, Ph.D., a research fellow in the Laboratory of Neurobiology, and Heping Cao, Ph.D., center, then a postdoctoral fellow. (Photo courtesy of Heping Cao)

Kennington, one of Kari's friends in the Peptide Hormone Group, returned to the patio after taking her turn with the shovel as French waited for the next participant. (Photo by Eddy Ball)

Calendar of Upcoming Events

- **July 2** in Rodbell, 10:00 - 11:30 — DIR Scientific Director Candidate Seminar featuring Perry Blackshear, M.D., D.Phil., speaking on "The TTP Family of Tandem Zinc Finger Proteins and Their Roles in mRNA Turnover"
- **July 2** in Rodbell A 2:00 – 4:30 — NCCU ITSSTEM (undergraduate STEM majors) visit
- **July 6** in Rodbell 9:00 – 10:00 — Frontiers in Environmental Sciences, speaker and topic TBA
- **July 10** in Rodbell 11:00 – 12:00 —Microarray Group Seminar Series, featuring Rick Fannin speaking on "Gene Expression Profiling in Whole Blood as a Surrogate Indicator of Liver Injury"
- **July 10** in E3162 2:00 – 4:00 — Seminar featuring Ben Rybick, Ph.D., speaking on "DNA Adducts in Prostate Cancer"
- **July 11** in Rodbell 11:00 – 12:30 — Summers of Discovery Seminar Series featuring Karen Adelman, Ph.D., speaking on "Stuck in the Starting Gates: Regulating Gene Expression by Holding Back Transcription Elongation"
- **July 12** in Rodbell 1:00 – 2:00 — Laboratory of Structural Biology Seminar Series featuring Lars Pedersen, Ph.D., speaking on "Better living through reduced entropy? Can mutation of a fusion lead to a better lattice?"
- **July 13** in Rodbell 9:00 – 10:00 — Frontiers in Environmental Sciences, featuring Steve Kleeberger, Ph.D.
- **July 17** in Rodbell 11:00 – 12:00 —Microarray Group Seminar Series, featuring Pierre Bushel, Ph.D., speaking on "Leveraging Bioinformatics Tools, Methodologies and Resources for Microarray and Genome Informatics"
- **July 18** in D450 11:00 – 12:30 — Summers of Discovery Seminar Series featuring Jonathan Freedman, Ph.D., speaking on "The Molecular Biology of Bugs, Worms, Fish and Mice"
- **July 19** in F193 1:00 – 2:00 — Laboratory of Structural Biology Seminar Series featuring David A. Schwartz, M.D.
- **July 24** 3:00 – 6:00 and **25** in Rall Mall — Summers of Discovery Annual Poster Session
- **July 25** in Rodbell 10:00 - 11:00 — Superfund Basic Research Program Distinguished Lecture Series, featuring Vas Aposhian, Ph.D.
- **July 27** in Rodbell 9:00 – 10:00 — Frontiers in Environmental Sciences, speaker and topic TBA
- **July 27** in Rodbell 1:00 – 4:00 — Summers of Discovery Awards Ceremony

Return to Table of Contents

e Factor
Your On-Line Source for NIEHS News

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*