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February 2007

NIEHS Spotlight

Science Notebook

Did You Know?

NIEHS Spotlight

NIEHS Hosts Children's Environmental Health Workshop

By Eddy Ball

On January 22 and 23, members of the public, grantees and adjunct specialists gathered in Rodbell Auditorium to propose new strategies for research in children's environmental health. The two-day workshop, titled "Children's Environmental Health Research: Past, Present and Future," looked at ways to enhance research and utilize best the resources available in a time of budgetary constraint. Discussion revolved around the ultimate goal of translating research findings into effective prevention and interventions. Additional information about the workshop, including a webcast of the event, is available online.

Schwartz welcomed workshop participants and reiterated the NIEHS commitment to supporting research in children's health. (Photo courtesy of Steve McCaw)

Workshop organizers, led by Director of the Office of Risk Assessment Research Chris Portier, Ph.D., planned the event to coincide with deliberations of an NIEHS working group charged with recommending funding strategies for future research in children's environmental health. These funding priorities are a topic of special interest for attendees affiliated with the Children's Centers jointly funded by NIEHS and the Environmental Protection Agency.

In his welcoming remarks, NIEHS Director David A. Schwartz, M.D., underscored the Institute's continuing support for children's environmental health research. "It fits entirely with our Strategic Plan," Schwartz asserted. "This conference is important because… [its findings] will be part of the deliberations of the group that will help set the course for children's environmental health research at our institute over the next five to ten years."

Portier charged attendees with the task of thinking critically about new research strategies. (Photo courtesy of Steve McCaw)

Making his charge to attendees, Portier described the two-day event as a "journey" into children's environmental health research that would take participants from lessons that can be learned from the past, to the accomplishments of the present and on into the future. The conference examined the epidemiology, mechanisms and clinical implications of four childhood diseases and disorders linked to environmental exposures: lead toxicity, asthma, metabolic disorders and attention deficit/hyperactivity disorder (ADHD). The organizing committee invited

leading American and European experts in children's health research to participate in the meeting's deliberations. In addition to workshop chair Phil Landrigan, M.D., of Mt. Sinai School of Medicine, who moderated the session on metabolic disorders, session chairs included Annette Kirshner, Ph.D., of NIEHS (Lead Toxicity); Harold Zenick, Ph.D., of EPA (Asthma); and Cindy Lawler, Ph.D., of NIEHS (ADHD).

Landrigan kept the two-day event on schedule and the participants focused on determining best practices in children's environmental health research. (Photo courtesy of Steve McCaw)

The workshop opened with discussions of the two areas, lead toxicity and asthma, that demonstrate the successful translation of research findings into evidence-based intervention and prevention strategies. According to panelists, progress in these areas became possible once investigators successfully established clear connections between environmental exposures and disease in children — developing a disease paradigm to drive translational efforts. Armed with these findings, public health advocates were able to present compelling arguments to raise general awareness of the need for measures to reduce exposures and develop intervention strategies.

Although ADHD and metabolic disorders also appear to have environmental causes, investigators still need to answer central questions about the disorders. Unlike research in lead toxicity and asthma, research in ADHD and metabolic disorders has yet to identify the specific environmental triggers involved. Consequently, researchers have not developed effective prevention and intervention strategies that are directly related to reducing or eliminating environmental exposures for these diseases.

Despite the striking differences in the four sessions, several common themes emerged during presentations and panel discussions. When Landrigan presented his concluding remarks at the end of the second day, he pointed to four areas where participants seemed to reach a consensus on priorities:

The panels were comprised of widely known experts in their respective fields. Pictured (left to right) are some of the major players in lead toxicity research over the past 35 years: Joseph Graziano, Ph.D., of Columbia University, Herb Needleman, M.D., of the University of Pittsburgh, Bruce Lanphear, M.D., of Cincinnati Children's Hospital Medical Center, and Tomas Guilarte, Ph.D. of John Hopkins University. (Photo courtesy of Steve McCaw)

- Creating interdisciplinary research teams that bring together investigators from different disciplines to achieve more rapid translation of research findings.
- Conducting more prospective studies, large and small, to demonstrate better the interplay between environmental exposure and the causes, mechanisms and effects of diseases over longer periods of time among well-defined cohort populations
- Encouraging "cross talk" among researchers from different disciplines working on the same kinds of problems in order to develop new partnerships in research
- Developing research paradigms to help investigators move more quickly toward results that can be translated into effective clinical and public health interventions

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DERT Success Story — Small Business Grantee Gets NIH Support

By Eddy Ball

Superfund Basic Research Program (SBRP) grantee Chang-Yul Cha, Ph.D., recently received a major business development boost with an invitation to participate in the NIH Commercialization Assistance Program (CAP). This recognition is a tribute both to Cha's ingenuity and to the foresight of grant administrators in the NIEHS Division of Extramural Research and Training.

Engineer and Inventor Chang-Yul Cha (Photo courtesy of C-Y Cha)

CAP, now in its third year, helps some of the most promising life science companies to bring innovative technologies to market. NIH chose Cha, a chemical and petroleum engineer, for the program based on his achievements in developing microwave chemical recovery equipment with extramural NIEHS funding through Small Business Innovation Research (SBIR) Phase I and Phase II grants.

Cha is the founder and president of the Cha Corporation in Laramie, Wyo. He developed and successfully operated his equipment for more than two months at the former McClellan Air Force Base in Sacramento, Calif. Established in 1935, McClellan was a major arming and storage facility for the U. S. Air Force. When it was closed in 1995, it became a business park, and parts of it were distributed to various federal agencies.

The chemicals used in aircraft maintenance, such as solvents, caustic cleaners, fuel oils and lubricants, caused extensive contamination at McClellan, particularly to its groundwater. Clean-up started in the 1980s. Remediation is still ongoing and expected to take at least another decade. McClellan provided an ideal venue to test Cha's new technology for improving clean-up at Superfund sites, eliminating the secondary air pollution produced in clean-up and making the process more cost effective.

Cha developed a method using microwave technology to recover solvents and other chemicals by adsorption from activated carbon used for cleaning up hazardous wastes. Activated carbon adsorbs chemicals in much the same way that charcoal incorporates lighter fluid: the fluids bind to the surface of the carbon in a thin layer — as opposed to filling the pores of a material as they would if *absorbed* by it. This quality of adsorption makes it possible for volatile organic compounds (VOCs) picked up by activated carbon from the air stream to be recovered as liquid and the medium reused.

The Cha microwave-based gas cleanup process exposes saturated carbon to microwave energy as it passes through a quartz tube reactor, where the medium is *desorbed* as vapors rise and become liquid in a two-stage water-cooled condenser system. In its use of energy to isolate VOCs, the process is similar to distilling purified water from tap water or alcohol from a fermented base. By restoring the original adsorptive capacity of activated charcoal, the process eliminates the need for supplying fresh material.

The self-contained system reduces expense in several other ways as well. It eliminates handling and transporting of contaminated carbon, saves energy by eliminating the natural gas used in conventional oxidizers, and recycles fuels and solvents that can be reused after processing. Finally, the equipment is portable, allowing it to be mounted on a trailer and moved from site to site as needed.

When work is finished at one site, a medium-sized truck can move the light-weight, portable Cha field-ready prototype microwave reactor system to a new location. (Photo courtesy of C-Y Cha)

CAP supports a select group of SBIR Phase II grantees over a ten-month period with assistance overcoming the obstacles and meeting the challenges involved in turning good inventions into commercially viable products. Cha and other program participants receive individual mentoring and attend a series of workshops on such topics as developing strategic alliances, identifying sources for funding, defining intellectual property rights, creating a long- and short-term marketing strategy, and building a management team.

In addition to guidance and mentoring on commercialization issues, CAP participants are in contact with a number of investors and industry representatives through the course of the program. At the end of the program, a select group of NIH-CAP companies present their technologies at the NIH Life Sciences Showcase, helping them reach a national audience of investors and industry leaders.

Thanks to Superfund grants, Cha's innovative technology for improving hazardous waste clean-up is several steps closer to becoming a marketable product. According to the SBIR program administrator for Cha's grant, Beth Anderson, Phase I and II grants complement the conventional notion of translational research by encouraging private sector development of life science technologies that can be applied to help prevent diseases by reducing exposures, thus creating a mutually beneficial public-private partnership.

"Dr. Cha's passion for advancing this very novel technology has been a real win for the program and holds great promise for numerous applications," Anderson said.

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Civil Rights Leader Julius Chambers Speaks at MLK Event

By Eddy Ball

The ice and snow on January 18th may have delayed the Main Event in the Celebration of the Life and Legacy of Dr. Martin Luther King, Jr., scheduled for 10:00 AM, but they failed to dampen the audience's enthusiasm for Keynote Speaker Julius Chambers, LL.D., LL.M. Ten minutes into the introductions, Environmental Protection Agency (EPA) and NIEHS employees had filled nearly all of the available seating in the conference rooms of the EPA main building.

Main Event Speaker Julius Chambers (Photo courtesy of Steve McCaw)

Bill Laxton, director of the Office of Administration and Resources Management EPA-RTP, introduced Chambers and offered a brief history of his accomplishments. A native of North Carolina, Chambers has been a "first" virtually all of his life. He

was the first in his law school class at UNC-Chapel Hill, the first African American to serve as editor-in-chief of the UNC Law Review, founder of the first African-American law firm and the first chancellor of North Carolina Central University (NCCU) to challenge the EPA on its record of civil rights compliance and environmental justice.

Chambers began his talk with a frank account of his criticism of EPA and his quest to persuade the agency to live up to its mission in regard to poor people and minorities. He denounced the agency in the early 1990s for what he saw as "intentionally discriminatory" employment practices and for its failure to combat "environmental racism" by not opposing the dumping of hazardous materials in poor and minority neighborhoods.

Director of the Office of Administration and Resources Management EPA-RTP Bill Laxton (Photo courtesy of Steve McCaw)

However, as a legal scholar, former Director-Counsel of the NAACP Legal Defense and Educational Fund (LDF) and a consummate negotiator, Chambers combined his criticism with an invitation for EPA and NCCU to partner in efforts to remedy the situation. As a consequence, EPA made strides to correct its shortcomings and aggressively promote minority involvement in science and environmental protection.

Chambers, who led the legal team in the landmark school busing case Swann v. Charlotte-Mecklenburg Board of Education (1971), reviewed the Supreme Court's recent decisions concerning the use of race as a consideration in correcting past discrimination. In the jurist's opinion, a gradual erosion of civil rights has been taking place in these decisions, a trend which challenges advocates of equal opportunity. "The threat [to equality] is real," he argued, "and it poses a serious problem for us."

Chambers countered his grim account, however, with a call for renewed efforts as he invoked the legacy of King and of Justice Thurgood Marshall, one of the speaker's predecessors at the head of the LDF. "To be sure, our problems are different [than theirs were]," he reminded the audience. "But we start with some advantages. We've at least seen that we can convince people to change." Chambers challenged the audience to see King and Marshall not as historical figures and icons of a movement whose time has past, but as leaders whose spirit can inspire people to take on the new challenges of today and tomorrow.

Near the end of his speech, Chambers challenged the EPA once again. "I want to take this opportunity," he said with a smile, "to present four proposals" for new partnership efforts between EPA and historically black colleges and universities (HBCUs):

- Designation of NCCU or other HBCUs as EPA research institutions with EPA research facilities

• Establishment of an EPA center to educate citizens about environmental needs, creating what Chambers called "citizen scientists"

• Utilization of empty EPA buildings in RTP as scientific facilities for NCCU

• Expansion of EPA collaboration with HBCUs to promote the recruitment and training of minority scientists

At 70, Chambers remains a vigorous and devoted advocate for what he sees as justice for all people — a country where individuals have rights to equal employment, equal housing, equal healthcare and equal environmental opportunities. For him, as for the other speakers at the event, Martin Luther King, Jr.'s birthday is, in the words of his wife Coretta Scott King, "Not a black holiday, but a people's holiday."

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Summer Intern Anirudh Kota to Participate in SOT Poster Session

By Eddy Ball

Cary Academy Upper School Science Chair Katy Allen, who teaches Chemistry, Human Anatomy and Physiology, will accompany Kota to the conference in Charlotte. (Photo courtesy of Steve McCaw)

2006 Summers of Discovery Intern Anirudh Kota has one of the best reasons ever to miss school next month. The Cary Academy junior and his chemistry teacher/mentor, Katy Allen, will spend March 26 and 27 in Charlotte. They will attend a workshop on "K-12 Education: Investing in the Future of Toxicology" and Kota will participate in the poster session at the Society of Toxicology Annual Meeting and ToxExpo.

The poster session will feature a study that scientists working with Neurotoxicity Group Director Jean Harry, Ph.D., conducted in the NIEHS Laboratory of Neurobiology. Kota was principal investigator on the study, titled "Comparison of injury-induced neurogenesis in young and aged mice." Harry served as corresponding author on the study, and Graduate Student/Technician Chris McPherson and Visiting Fellow Mineyoshi Aoyama, M.D., Ph.D., worked with Kota and Harry as co-investigators.

Near the end of his internship, Kota was a winner in the Summers of Discovery poster session. Last fall, the Science Day Awards committee invited the young scholar to return for the annual NIEHS event. His abstract appeared among the rows of abstracts by post-doctoral fellows displayed in the lobby outside Rodbell Auditorium, and, like his older, credentialed colleagues, Kota answered questions about his work from NIEHS scientists, visitors and judges.

Kota began his summer at NIEHS with the basics, learning how to slice, stain and photograph, reading the studies that Harry sent his way and mastering the lexicon of laboratory science and toxicology. According to McPherson, often Kota was able to complete his learning assignments in half the time expected. "He picked up things quickly, and he kept coming back for more work," commented McPherson. "We kept giving him more responsibility, and we probably could have given him even more."

Kota's Summers of Discovery supervisor/mentor Jean Harry. (Photo courtesy of Steve McCaw)

For the young chemist, getting the internship at NIEHS was a dream come true. "I was surprised when I went in for the interview and Jean did not even know she had spots, but she said up front, 'If I have a spot, it is yours.' I was very surprised and ecstatic. When I got home, I started jumping up and down like I'd gone crazy."

Both of Kota's parents work in scientific careers, his mother as a computer engineer and his father as a pharmacist, and they have encouraged his interest in science. Over the years, their son developed a love for chemistry and plans to pursue a career that involves working in that field. For his next move after high school, he's considering Duke and the University of North Carolina at Chapel Hill, and he's also looking into the seven-year medical program at East Carolina University.

Back at Cary Academy after his summer at NIEHS, Kota is taking Advanced Placement Chemistry and pursuing his several additional interests. Along with maintaining a high grade point average and making the honor roll, he is an enthusiastic athlete, excelling in basketball and soccer, an avid reader and an award-winning debater in tournaments sponsored by the National Forensics League.

Harry and Kota's colleagues at NIEHS were very pleased with the quality of his work — and even more importantly, with his attitude. Kota impressed his supervisor as being "very pleasant to work with, very responsible and very interested in what he was doing," Harry observed. "[Anirudh] seemed to be doing it [Summers of Discovery Research] more because he was interested in learning than in doing it for something to put on an application to college."

When it comes to the summer of 2007, Kota doesn't have set plans yet. He'd like to return to NIEHS if the program will let him, and Harry would like to have him back. "He was outstanding," Harry concluded. "He asked good questions and wanted to do things right, not just impress people."

Kota A, McPherson CA, Aoyama M, Harry J. Comparison of injury-induced neurogenesis in young and aged mice.

Recent work has identified proliferation of new neurons as a common feature of the adult brain. Neurogenic sites include both the subventricular zone and the subgranular layer/zone (SGZ) of the dentate gyrus (DG) as sources of stem cells and progenitor cells. While neurogenesis occurs at a low basal level in the normal brain, the generation of new cells can be stimulated by both synaptic activity and injury. This process declines as a normal process of aging. In the current study, we examined the level of neurogenesis within the SGZ both under normal basal conditions and following a focal injury to the neurons of the dentate gyrus. Using this model, we compared the level of neurogenesis in weanling mice (21-days-old) with the process occurring in the aged mouse brain (1 yr old). Mice received an acute ip injection of the hippocampal toxicant, trimethyltin (TMT) followed by bromodeoxyuridine (BrdU) at 50 mg/kg/bid/ip for 3 days. The level of neurogenesis was examined histologically and the differentiation of newly generated cells was identified by co-immunofluorescent staining with markers for neurons (NeuN). While injury induced neurogenesis and the differentiation to mature neurons occurred in the aged brain, it was significantly decreased as compared to the young. The distribution pattern of the new neurons within the dentate gyrus was also slightly altered over this time period. Using this model, we will continue to examine the differentiation of new cells to other cells types and by comparison as a function of aging.

Summer Intern Alexandra Levitt is Lead Author on ATC Pulmonary Study

By Eddy Ball

Last August, high school senior Alexandra Levitt returned to classes with more than memories of a good time during her summer in RTP and a technological edge in senior biology classes. When she went back to school in Philadelphia after working on a study of airway responsiveness at NIEHS, she could look forward to presenting the results of her summer's work in May at a poster session at the 2007 American Thoracic Society's 2007 International Conference in San Francisco.

Levitt clowns in front of the LRB staff photo board. (Photo courtesy of Dianne Walters)

Under the direction of Laboratory of Respiratory Biology (LRB) Chief Steve Kleeberger, Ph.D., and post-doctoral fellow Dianne Walters, Ph.D., who served as her mentor, Levitt explored a research interest she had developed during the previous summer, when she worked in drug development for a pharmaceutical company. Levitt, who plans to study medicine, examined the effects of the neurotransmitter serotonin on airway responsiveness in strains of inbred and chromosome-substitution strains of mice.

She worked with Kleeberger and Walters on the study, and several additional LRB colleagues contributed to the study, including Biologist Wesley Gladwell, Contract Biologist Jessica Martin and Technician Katharine Holder. The study showed such good potential that Walters, Gladwell and Martin will continue work on the study and hope to publish a journal article further exploring the genetic aspects of lung response to serotonin, which will credit Levitt as one of the contributing authors.

Levitt was one of 18 high school participants in the NIEHS Summers of Discovery Research Program. She is a student at the Springside School in Philadelphia, which she has attended since ninth grade, and lives with her family in the nearby township of Horsham. Her father, who is a physician, knew of Kleeberger's laboratory at NIEHS and suggested she apply to the program and stay with relatives in the area.

"Summers of Discovery was a great program," Levitt said. "It was amazing to work with a Ph.D. scientist who knew so much and spent so much time with me." Being at NIEHS, with its state-of-the-art equipment and facilities, "showed me how big environmental medicine is and how it interacts with so many other medical fields." Working with Walters was an important part of her NIEHS experience. Walters was a mentor for the young investigator, helping her learn laboratory basics and design the study, and a good role model.

Levitt said that she has always been drawn to medicine and its potential for helping people. She credits her family with encouraging her to pursue her interest in science. She also appreciates the way her small, all-girls school nurtured her and her classmates in the ninth and tenth grades before putting them together with boys in junior and senior science classes. "It was the best of both worlds," she observed. "I had a chance to build up my self-confidence, and by the time I had to be in a class with boys, I was ready for it."

Levitt's Summers of Discovery mentor Dianne Walters (Photo courtesy of Steve McCaw)

Authoring a study presented at an international conference is obviously an important accomplishment for an aspiring scientist, and no doubt the study will impress college admissions officials. However, Levitt is more than a scientist; she has a broad range of interests and achievements that should impress any college she chooses. She writes and draws, enjoys volleyball and horseback riding, has volunteered at a riding program for disabled children and is the editor of her school's literary magazine.

The summer's work was also rewarding for Walters, who was impressed by the intern's attitude toward the challenges of working in the lab. "This was a good mentoring opportunity for me," Walters said. "It's unusual to find a high school student who not only has a high level of knowledge, but also an interest in the work and a dedication to doing the best job she can."

Levitt recently attended a five-day writing retreat in Montana and stays very busy with extracurricular opportunities through her school and community. As she looked ahead to what she'll do this summer, she talked of more personal time than she's had for years. "I want something less structured this summer," she said.

Levitt A, Gladwell W, Walters DM, Martin JR, Holder K, Kleeberger SR. Inter-strain variation in airway responsiveness to serotonin. NIH/NIEHS, RTP, NC

Introduction: Airway hyperresponsiveness (AHR) is a hallmark of asthma and other chronic respiratory conditions. Studies examining AHR to cholinergic agonists have identified quantitative trait loci (QTLs) on several chromosomes; however, few studies have investigated the genetic basis of AHR to serotonin (5-HT), a potent bronchoconstrictor released from mast cells. The current study was designed to identify the genetic basis of differential susceptibility to 5-HT-induced AHR in inbred mice.

Methods: Fifteen inbred strains of male mice (JAX) were assessed for changes in pulmonary function in response to 5-HT using the flexiVent® system. Briefly, mice were anesthetized, cannulated, paralyzed and ventilated at 150 breaths/min with a tidal volume of 7.5 ml/kg. Airway resistance was measured every 30 sec for 5 min after a 10 sec aerosol of 5-HT (10 mg/ml) or phosphate buffered saline (PBS). Peak resistance values were reported as the mean + SEM for each strain (n=6-8/strain).

Results: A comparison of inbred strains revealed significant inter-strain variation in 5-HT-induced airway resistance. C3H/HeJ mice were the least responsive and BTBR T+ tf/J mice were the most responsive to 5-HT (1.0650 cmH2O.sec/ml vs 16. 9327 cmH2O.sec/ml, respectively). There were no significant differences in airway resistance at baseline or in response to aerosolized PBS between strains.

Conclusions: Differential responses in inbred strains of mice indicate that there is a significant genetic contribution to 5-HT-induced increases in resistance. Future studies will identify the mode of inheritance and candidate genes for this model.

Funded by NIEHS Intramural Program.

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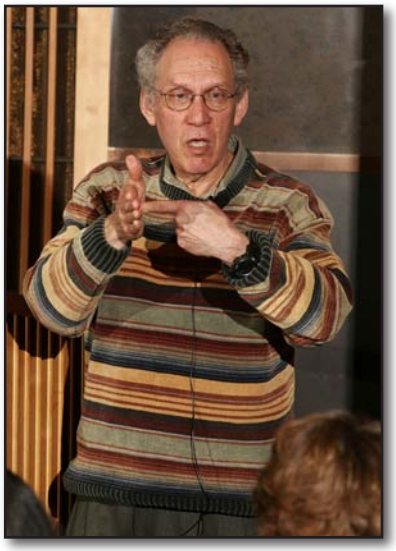
Science Notebook

DNA Repair Expert Delivers Distinguished Lecture

By Eddy Ball

Geneticist James Haber, Ph.D., presented the most recent talk in the 2006-2007 NIEHS Distinguished Lectures series at 11:00 AM on January 9 in Rodbell Conference Center. Haber is the Abraham and Etta Goodman Professor of Biology and director of the Rosenstiel Basic Medical Sciences Research Center at Brandeis University. His lecture addressed "Checkpoint Responses and Repair of a Broken Chromosome."

Laboratory of Molecular Genetics Staff Scientist Dmitry Gordenin, Ph.D., sponsored Haber's talk. In Gordenin's introduction, he described Haber as "the centerfold of molecular genetics" and a leading authority on the subject of double-strand DNA breaks (DSBs). "To a large extent we owe the current knowledge about the molecular mechanisms of DSB-repair to the work of the Haber lab," Gordenin said. "[Haber's] experimental approach and the system itself have been very successfully utilized in a number of laboratories."



Geneticist James Haber
(Photo courtesy of Steve McCaw)

Haber's lab uses yeast, specifically the budding yeast, *Saccharomyces cerevisiae*, as an experimental organism to study DSBs *in vivo*. This yeast possesses many characteristics of more complex organisms, yet offers the advantages of studying a simpler, unicellular living system. The repair process is well conserved through evolution, and studies of DNA repair homologs in yeast and other simple organisms can help scientists understand the process in human cells.

Radiation, reactive oxygen species and replication errors or "nicks" constantly threaten damage to DNA. DSBs are

An Obligation that Began a Career in Genetics

In a "Perspectives" commentary published in the July 2006 issue of the journal *Genetics*, Haber described the turn of events that thrust him into the field of genetics. "When I arrived at Brandeis [as an assistant professor of Biology]," he explained, "I was assigned to teach genetics, a subject I had never studied as either an undergraduate or a graduate student."

Luckily for him, the university had teamed Haber with master geneticist Jeff Hall, who guided the new teacher through *Drosophila* and maize genetics and introduced him to the classic genetic experiments of the 1930s performed by Lillian Morgan and Barbara McClintock. Haber's experiences teaching the course he had never taken, along with an intensive three-week yeast genetics course at Cold Spring Harbor Laboratory in 1970, sparked his career-long quest to elucidate genetic processes.

What he learned during that time established the foundation for a series of major contributions to the field. Over the course of his career Haber has made groundbreaking discoveries concerning the repair of DSBs, especially by developing methods to observe DNA repair in real time. He has demonstrated links between DNA repair and normal DNA replication and investigated how DNA-damaged cells resume mitosis after repair.

Today, Haber still appreciates the value of his obligatory undergraduate courses as learning experiences for himself, describing them as "forays into the 'beyond' [that] were instrumental in moving my research in new directions."

the most toxic DNA lesions and DSB-repair is the last line of defense against DNA damage to the genome. To survive and reproduce, cells must assess damage to DNA and then repair it or trigger apoptosis to eliminate damaged cells and protect the viability of the organism. Studying the mechanisms of repair of DSBs in this budding yeast – and especially the defects in repair of chromosome damage or defects in what is known as the DNA damage checkpoint – can offer insight into what Haber described as "the incredible genome instability" of cancer cells.

Lecture Sponsor Dimitry Gordenin (Photo courtesy of Steve McCaw)

To repair DSBs, cells respond by activating the DNA damage checkpoint, which includes the induction and repression of many genes. The checkpoint triggers an arrest in the cell cycle to allow the organism to repair the damaged chromosome by searching initially intra-molecularly and, then if necessary, extra-molecularly through the entire genome, for competent material to make the repair.

When the repair has been completed successfully, the checkpoint arrest signal is extinguished and reproduction continues as cells re-enter the cell cycle. Checkpoint defects cause a substantial problem in multi-cellular organisms because damaged chromosomes and genetic instability can result in tumors. An understanding of checkpoint function can shed light on the mechanism of tumor formation and cancer predisposition and ultimately may provide insights into new therapeutic targets for cancer treatment.

Haber and his colleagues have made significant progress toward understanding the roles of DNA intermediates that arise during the repair of DSBs by recombination, as well as during meiosis and mating type switching. His lab has established the relative importance of several pathways for non-homologous end-joining in yeast and shown their similarity to those in mammalian systems. However, despite the advances his lab has made in elucidating DSB repair, Haber admitted, "Every time you think you understand these processes, like resection, something else gets in the way."

In the course of his career, Haber has received many honors for his work. In 2005, he was elected a fellow of the American Association for the Advancement of Science (AAAS), and for over a decade he has been a fellow of the American Academy of Microbiology. Several funding organizations, including the Sloan Foundation, the Guggenheim Foundation and the National Science Foundation, have provided support for his research. Individually and with colleagues worldwide, he has published over 200 articles in peer reviewed journals, and he serves on the editorial boards of several important journals in his field, including *Molecular and Cellular Biology, DNA Repair, PLoS Biology* and *PLoS Genetics*.

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LMG Researcher Reports on Clinical Trial of Antioxidant in Friedreich's Ataxia

By Eddy Ball

At his lecture on January 10 in Rall D-350, Laboratory of Molecular Genetics Principal Investigator Ben Van Houten, Ph.D., reported on the results of his group's recent collaboration with researchers from a sister institute in a phase 2 double-blind, placebo-controlled clinical trial. Utilizing advanced technology available at NIEHS, the team completed studies of gene expression that show potential for clinical application in monitoring patient response to treatment.

The study examined the efficacy of an antioxidant intervention, idebenone, for Friedreich's ataxia, a progressive neurological disease. As part of an NIH Bench-to-Bedside award, teams of intramural researchers from NIEHS, led by Van Houten, and the National Institute of Neurological Disorders and Stroke (NINDS), led by Nicholas Di Prospero, M.D., Ph.D., and Kenneth Fischbeck, M.D., evaluated clinical and molecular endpoints in the first clinical trial of its kind involving the controversial alternative treatment.

The collaborative study followed 48 subjects, aged 9 to 11 and 12 to 17 years, in four treatment arms over a period of six months. Participants received placebo, low, intermediate or high doses of the antioxidant. Because of restrictions on drawing blood from healthy children for clinical trials, researchers used a group of ten 18- to 25-year-old healthy individuals as controls.

All of the subjects had manifest symptoms of the neurological disorder, an iron-homeostasis disease caused by a mutation

Friedreich's Ataxia

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

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

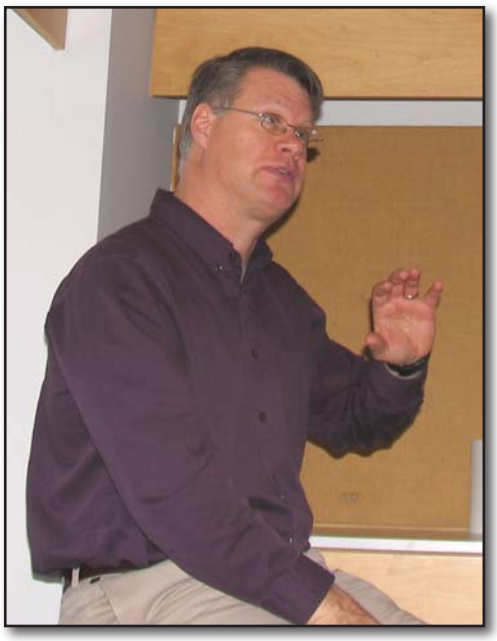
As Friedreich's ataxia progresses in patients, they may lose the muscle control necessary to speak, read or walk. Although the rate of progression of the disease varies, many patients are forced to use a wheelchair a decade or two after symptoms appear and eventually may become completely incapacitated.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

There is no cure for the disease, and, although some of the symptoms can be treated with medications or physical therapy, currently available treatment does little to increase lifespan or improve patients' diminishing quality of life.

In addition to the clinical trial conducted by NINDS/NIEHS, researchers at the Necker Hospital in Paris are currently recruiting volunteers for a study on the efficacy of iron chelation to improve central nervous system function.

Idebenone

Idebenone is an analogue of CoQ10, a far better known and more popular over-the-counter antioxidant, but it is even more effective at inhibiting lipid peroxidation and has been shown to stimulate cardiac function. Many parents self-administer their Friedreich's ataxia children with the compound because the sale of idebenone is not regulated by the FDA, and they can purchase the supplement without restriction on the web. Practitioners in Japan have used the compound with Parkinson's and Alzheimer's patients, and there are many anecdotal reports of its efficacy in ataxia disorders, possibly by enhancing electron transport in the mitochondria.



LMG Principal Investigator Ben Van Houten (Photo by Eddy Ball)

in the gene for frataxin, an iron-binding protein. In patients with Friedreich's, frataxin is not sufficiently available to load iron, starving cells of the mineral and leading to the accumulation of iron in the mitochondria.

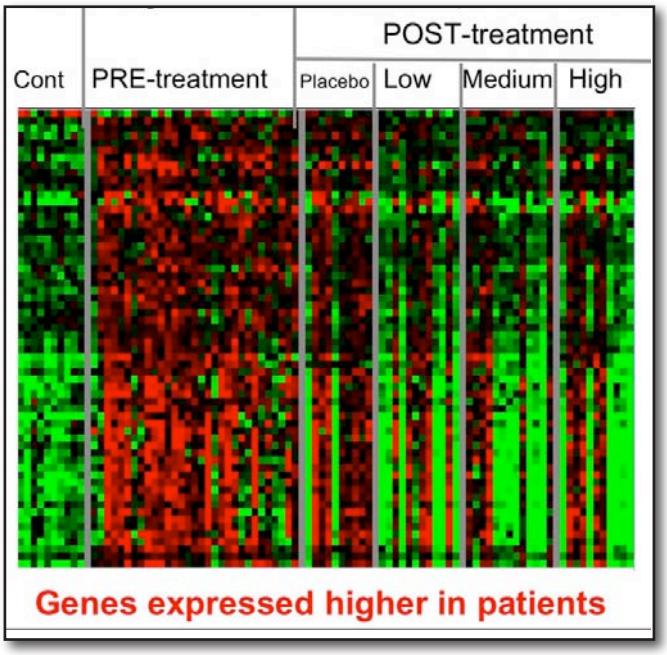
The teams conducted the study at the NIH Clinical Center in Bethesda, where over a period of two days subjects underwent a battery of testing and sample collection for laboratory studies. The tests included a very sophisticated cardiac output assessment, several different measures of gait and a number of neurological batteries. Testing and sample collection took place at the beginning of the study and six months later. The researchers drew blood for RNA, DNA and serum analysis and collected urine samples.

Van Houten and colleagues in his lab took RNA from lymphocytes and performed gene expression profiling at NIEHS. They also sent serum and urine to a contract lab for metabolic profiling and analysis of low molecular weight metabolites. Using lymphocytes as a surrogate marker for damage to heart tissue, the researchers looked for evidence of chronic mitochondrial DNA damage from cumulative free radical oxidation and iron overload.

Using Significance Analysis of Microarray, the NIEHS team determined that there were 6,000 gene expression changes that differed between controls and subjects. Researchers employed ANOVA analysis to narrow that number to the 600 most significantly different genes. They then selected a set of 142 genes that could give researchers the most information about differences between patients and controls and between pre- and post-treatment gene expression.

Looking at the results, the researchers discovered that the gene expression patterns of most of the low-, medium- and high-dose subjects showed patterns similar to controls after treatment, while the placebo group's results looked the same as or worse than treatment subjects' results prior to dosing. There were a small number of non-responders, but the averaged gene expression data confirmed the efficacy of treatment, the blunting of the pro-inflammatory state and the dose-dependency of response. This study is especially exciting, according to Van Houten, because heretofore the pro-inflammatory state of these patients had not been fully appreciated and the study suggests a potential new strategy for therapy.

Significantly, the gene expression outcomes corresponded to the clinical and metabolic outcomes. Neurological measures showed improvement in gait and motor control,



This figure is a tree-view rendering of microarray data, showing supervised clustering of some of the 142 most significantly changed genes (red indicates induced, green repressed) in Control (Cont) subjects and Friedreich's patients before and after treatment with idebenone. Note the dramatic contrast between pre-treatment/placebo results (predominantly red) and the post-treatment dose-dependent increases in green. (Graphic courtesy of Ben Van Houten. mRNA hybridizations on to oligonucleotide microarray chips performed at NIEHS by Rick Fanin; gene expression analysis conducted by Astrid Haugen of NIEHS and Joel Parker of Constella Group).

and there were significant changes in metabolites measured in serum and urine. Van Houten's lab also identified nine "responder" genes whose expression may help discriminate between patients who are benefiting from treatment and patients who are not responding to the intervention.

The clinical trial produced surprising results for Van Houten and his team. He explained, "We saw a really big difference between patients and controls at the beginning of the study, and that was exciting. We also could track changes in gene expression that corresponded with treatment and to improvements in clinical measures."

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Guest Lecturer Discusses Glia Signaling and Neurotoxicity

By Eddy Ball

On January 11 in Rall F-193, National Institute for Occupational Safety and Health (NIOSH) scientist James P. O'Callaghan, Ph.D., presented a lecture jointly sponsored by the Laboratory of Pharmacology and Chemistry (LPC) and the Laboratory of Molecular Toxicology. O'Callaghan spoke to a capacity audience on "Neurotoxicity Due to MPTP and Methamphetamine: Glia Signaling and a Role for TNFα."

Following the lecture, LPC Senior Investigator David Miller, Ph.D., right, discusses the research model with O'Callaghan, left, and Hong. (Photo by Eddy Ball)

LPC Supervisory Pharmacologist John Hong, Ph.D., was the lecture host. O'Callaghan is the head of the Centers of Disease Control (CDC) Molecular Neurotoxicology Laboratory. He is also the CDC Distinguished Consultant at the Toxicology and Molecular Biology Branch of the NIOSH Health Effects Laboratory Division. The lecture was the first of three he presented at NIEHS and EPA during his visit to the RTP campus.

O'Callaghan's presentation focused on the role of microgliosis in chemically induced neurotoxicity. Microgliosis refers to the activation of microglia, non-neural cells in the central nervous system, in the earliest stages of disease. In response to the presence of neurotoxin in the brain, microglia mount an immune-like response in the central nervous system to defend the organism and initiate a cascade of events that lead to striatal dopaminergic nerve terminal damage and dopamine (DA) depletion.

Two compounds that researchers have studied in regard to microgliosis are MTPT, a neurotoxin that produces Parkinson's-like symptoms, and methamphetamine (METH), a widely used street drug. Understanding the glial response following injury is important for discovering pharmacological antagonists that can modulate or even block the effects of neurotoxic exposures and help preserve normal dopamine synthesis.

In their studies of MTPT and METH neurotoxicity, O'Callaghan and his colleagues used a single dose of neurotoxin to reduce dopamine levels in laboratory animals to about 50 percent of normal. The single-dose regimen produces a moderate degree of neurotoxicity and allows researchers to measure changes over short periods of time. This model also permits a closer examination of the disease process by eliminating the confounding effects that can occur with multiple dosing. Unlike much of the research on neurotoxicity

in cell loss models, O'Callaghan's research focused on early stage nerve terminal damage and glial response that occur over a 48- to 72-hour period.

These investigations have sought to identify the cellular events that activate microglia and signals of activation by using protein immunoassays to pinpoint molecular markers to serve as guides for intervention. The investigators found that one of the central proteins whose levels increased in reaction to chemically induced neural damage was glial-fibrillary acidic protein (GFAP), which is a marker for astroglia.

O'Callaghan hypothesized that an increase in GFAP, which is evident as early as six hours after dosing, would be a simple indicator of neurotoxicity and the best marker for neurodegeneration. In a series of experiments, he demonstrated that induction of GFAP paralleled neurotoxicant-induced reductions in striatal levels of DA and its synthesizing enzyme, tyrosine hydroxylase. Conversely, treatment with a known neuroprotective agent, such as the dopamine reuptake inhibitor nomifensine, corresponded to a drop in GFAP levels and an increase in DA and tyrosine hydroxylase.

Using the same model to study the role of the pro-inflammatory cytokine tumor necrosis factor alpha (TNFα) in neuropathology at nerve terminals, O'Callaghan's team found a pattern of TNFα induction after dosing, but prior to increases in levels of GFAP. Treating with nomifensine, they were able to block TNFα before microglial activation could occur.

Because of the involvement of TNFα induction so early in striatal dopaminergic neurotoxicity, the cytokine may be a promising target for intervention. However, O'Callaghan emphasized that researchers need to understand more about the cascade of events involved in MTPT and METH neurotoxicity. Some pro-inflammatory cytokines and chemokines may have region-selective effects in the brain. TNFα, for example, performs a dual role in the brain, as a promoter of neurodegeneration in striatum and as a protector against neurodegeneration in the hippocampus.

Nevertheless, the ability to measure microglial activation in its earliest stages and the identification of a target cytokine are major steps forward in understanding how to protect against the effects of MTPT- and METH-induced neurotoxicity. Further study of biomarkers and neuroprotective agents, such as the antibiotic minocycline, should help scientists pair the most effective agents to specific neurotoxicants, target sites and dose responses.

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DERT Papers of the Month

By Jerry Phelps

Predictive Gene Also Maintains Differentiation of Mammary Ductal Cells

A gene known as GATA-3 is in a family of genes responsible for driving the processes that take stem cells down the path of differentiation that lead to mature cells regardless of their ultimate fate. NIEHS-supported researchers at the University of California San Francisco have now determined that GATA-3 is also required for the maintenance of differentiation in ductal cells of the mammary gland.

Cancer researchers know that breast tumors with high GATA-3 expression have a good prognosis. The cancers tend to be well-differentiated, and the cells maintain many characteristics of normal mammary cells including high numbers of estrogen receptors. In contrast, cancers with low expression of the gene tend to be diffuse and poorly differentiated and lead to poor prognosis for the patient. The new research offers clues to why this is so.

Mammary ductal cells, also known as luminal cells, line the mammary ducts that carry milk during lactation. They are a primary site in the mammary gland for cancers to form. The research suggests that the loss of functioning genes and the subsequent failure to maintain the mature state of the cells is what leads to the loss of differentiation and uncontrollable proliferation during cancer progression.

The new finding suggests that the gene may play a key role in the development of breast cancer and possibly other malignancies.

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

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Effects of Low-level Arsenic on Hormone Activity

Arsenic is known to be acutely toxic at moderate to high doses and to cause a wide variety of adverse health outcomes at relatively low doses. New research findings from the NIEHS Superfund Basic Research Program-supported laboratory of Josh Hamilton at Dartmouth Medical School shed light on a possible mechanism by which arsenic may produce its varied effects.

Previous research by this lab showed that arsenic disrupted glucocorticoid receptor mediated gene transcription in a biphasic manner: at drinking water levels near the current EPA standard (5-50 parts per billion) arsenic enhanced the hormone-stimulated gene expression, but at slightly higher doses (50-200 parts per billion) it almost completely blocked hormone-stimulated receptor gene expression. The new research findings demonstrated the same effects with progesterone, a steroid hormone involved in female reproduction, and mineralocorticoid hormone, a steroid hormone responsible for salt and water metabolism and balance.

This study determined that arsenic, unlike most endocrine disruptors, does not activate the receptors by mimicking the natural hormone, nor does it block the natural hormone from binding to and activating its

specific receptor. The investigators also found that arsenic does not inhibit the movement of the hormone-activated receptor into the nucleus of the cell to bind to DNA and initiate gene expression.

Citation: Bodwell JE, Gosse JA, Nomikos AP, Hamilton JW. 2006. Arsenic disruption of steroid receptor gene activation: Complex dose-response effects are shared by several steroid receptors. *Chem Res Toxicol* 19(12):1619-1629.

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Epoxide Hydrolase Inhibitors Effective for Cardiac Hypertrophy in Mice

Cardiac hypertrophy is defined as a thickening the of the heart muscle often as a result of high blood pressure. The heart muscle grows larger to compensate for the added stress of pumping blood against the increased pressure. Over time this condition can result in a weakening of the heart and can lead to congestive heart failure. New research supported by NIEHS in the laboratory of Bruce Hammock at the University of California Davis sheds light on a possible treatment to prevent heart enlargement.

Previous work by Hammock and his collaborators demonstrated that inhibition of an enzyme called epoxide hydrolase lowered blood pressure and lessened kidney damage in a laboratory animal model. The new research findings show that epoxide hydrolase inhibitors block an immune system protein, known as NF-κB, which plays a role in cardiac hypertrophy and accompanying arrhythmia. The inhibitors were effective in preventing and reversing cardiac hypertrophy in a mouse model.

These findings show that by blocking the pathway leading to the overgrowth of cardiac muscle, preventing the progressive deterioration of heart function is possible. This work could lead to new therapies for treating enlarged hearts and heart arrhythmias—conditions that currently require more invasive treatment options and ultimately progress to heart failure and sudden cardiac death.

Citation: Xu D, Li N, He Y, Timofeyev V, Lu L, Tsai HJ, Kim IH, Tuteja D, Mateo RK, Singapuri A, Davis BB, Low R, Hammock BD, Chiamvimonvat N. 2006. Prevention and reversal of cardiac hypertrophy by soluble epoxide hydrolase inhibitors. *Proc Natl Acad Sci U S A* 103(49):18733-18738.

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Identification of CRP Variants and Association with Serum Levels

C-reactive protein (CRP) is a marker for inflammatory processes. More recent research demonstrates that an elevated CRP level is also a risk factor for diabetes, hypertension and cardiovascular disease, and that genetic variation within the gene coding for the protein may be associated with levels circulating in the blood stream. A new study from the University of Washington partially supported by NIEHS confirms that genetic variations in the gene for CRP are associated with increased serum levels in the general population.

The study participants were part of the National Health and Nutrition Examination Survey (NHANES). DNA analyses were conducted on 7,159 participants. Genotyping was performed on all samples for nine single nucleotide polymorphisms previously found in the CRP gene. Several of the genetic variations for increased

and decreased CRP levels were more or less prevalent in different racial groups making up the study participants.

These findings are important because they confirm that serum levels of CRP are genetically influenced. The genetic variations identified in this study could be used to identify people at risk for cardiovascular and other serious diseases or to target people for more aggressive interventions to prevent heart disease from occurring.

Citation: Crawford DC, Sanders CL, Qin X, Smith JD, Shephard C, Wong M, Witrak L, Rieder MJ, Nickerson DA. 2006. Genetic variation is associated with C-reactive protein levels in the Third National Health and Nutrition Examination Survey. *Circulation* 114(23):2458-2465.

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DIR Papers of the Month

By Eddy Ball

Nicotinic Acetylcholine Receptors in Amygdala Section of the Brain

Two Laboratory of Neurobiology investigators have demonstrated for the first time the presence of functional α7-containing nicotinic acetylcholine receptors (nAChRs) in the rat basolateral (BLA) amygdala complex, which is located within the limbic system. In their NIEHS-funded study published in the *Journal of Physiology*, Rebecca Klein, Ph.D., and Jerrel Yakel, Ph.D., postulate that these receptors are likely to have an important role in the emotionally mediated aspects of nicotine addiction and working memory performance.

The researchers performed their experiments on acute amygdala slices from 14- to 21-day-old-rats within six hours of preparation. They performed whole-cell patch-clamp electrophysiological recordings on neurons in acute slices to identify the presence of functional nAChRs in BLA. Pressure application of acetycholine and laser-induced photolysis of caged-carbachol indicated that functional somato-dendritic nAChRs are present within the lateral and BLA nuclei. Using an α7-selective antagonist, Klein and Yakel also confirmed that the nAChRs in BLA complex are predominantly α7-containing.

The researchers concluded that “this information is critical as it might provide insight into the basic mechanism involved in various human disorders, such as anxiety, schizophrenia, epilepsy, addiction and autism.” In addition, it offers insight into the effects of nicotine on behavior and contributes to the search for effective therapeutics for treating these devastating conditions.

Citation: Klein RC, Yakel JL. 2006. Functional somato-dendritic α7-containing nicotinic acetylcholine receptors in the rat basolateral amygdala complex. *J Physiol* 576(Pt 3):865-872.

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NAG-1 Over-expression Protects against Intestinal Tumors

In an NIEHS-funded study published in the journal *Gastroenterology*, a team of intramural investigators report on the anti-tumorigenic effects of over-expression of nonsteroidal anti-inflammatory drug-activated gene NAG-1) in transgenic mice.

The investigators developed a transgenic mouse (NAG-Tg^{+}) expressing the human form of a protein called NAG-1 to analyze the effect of the gene's expression in preventing intestinal tumor development *in vivo*. They evaluated two colorectal carcinogenesis models in NAG-Tg^{+} mice to determine the efficacy of NAG-1 over-expression.

The team used a known intestinal carcinogen, azoxymethane, to induce tumors chemically and an intestinal tumor-specific genetic mutation (Apc^{Min+}) to induce cancer genetically in NAG-Tg^{+} mice and controls. Both groups of NAG-Tg^{+} mice showed a greater than 50% reduction in intestinal cancer, confirming the tumor suppression activity of NAG-1. In addition, they demonstrated the efficacy of overexpression in genetically induced tumorigenesis and reported that there were no apparent side effects associated with the intervention.

By elucidating the specific role of NAG-1 gene over-expression, the study's findings may have important consequences in the clinical setting. Colorectal cancer is one of the most common cancers and is responsible for the deaths of over 50,000 Americans each year.

Citation: Baek SJ, Okazaki R, Lee SH, Martinez J, Kim JS, Yamaguchi K, Mishina Y, Martin DW, Shoieb A, McEntee MF, Eling TE. 2006. Nonsteroidal anti-inflammatory drug activated gene-1 over expression in transgenic mice suppresses intestinal neoplasia, *Gastroenterology* 131(5):1553-60.

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Role of Estrogen Receptor-α in Gonadotropin Regulation

In a study published in the *Journal of Endocrinology*, a team of Laboratory of Reproductive and Developmental Toxicology investigators collaborated with a Lock Haven University researcher supported by the NIEHS Summers of Discovery Research Program to elucidate the effects of estrogen receptor-α (ERα) on gonadotropin synthesis and secretion. The authors of the NIEHS-funded study demonstrated that estradiol (E_2)-mediated negative feedback on the hypothalamic-pituitary (HP) axis is an ERα specific action.

The team of researchers conducted three experiments on groups of adult wild-type (WT) and ERα-null (αERKO) mice. All subjects were also genotyped by PCR on DNA extracted from tail biopsies. Experiment 1 involved determining basal levels of hypothalamic gonadotropin-releasing hormone, pituitary gonadotropin, plasma gonadotropin, and serum and plasma inhibin-A levels in intact animals. In Experiment 2, the team injected ovariectomized adult female WT and αERKO mice with vehicle or E_2 to determine effects on plasma gonadotropin and pituitary gonadotropin gene expression *in vivo*. The final experiment examined the effects of E_2 on lutenizing hormone secretion in dispersed pituitary cell cultures.

This study contributed significantly to the understanding of the mechanisms and precise sites of action by which estrogens exert both negative and positive effects on the HP axis, processes which are critical to reproductive function in mammals.

Citation: Lindzey J, Jayes FL, Yates MM, Couse JF, Korach KS. 2006. The bi-modal effects of estradiol on gonadotropin synthesis and secretion in female mice are dependent on estrogen receptor-alpha. *J Endocrinol* 191(1):309-317.

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Novel Pathway for Glucocorticoid Regulation of TNFα

A recent study by Laboratory of Signal Transduction Investigators Kathleen Smoak, Ph.D., and John Cidlowski, Ph.D., presented evidence for the first time of a new anti-inflammatory pathway for glucocorticoids by means of induction of tristetraprolin (TTP) mRNA and protein synthesis, which differs from classical anti-inflammatory pathways. The NIEHS-funded research appeared in the December issue of the journal *Molecular and Cellular Biology*.

To demonstrate this new pathway, Smoak and Cidlowski used the glucocorticoid dexamethasone to induce the synthesis of TTP mRNA and protein in human A549 lung epithelial cells and in lung, thymus, liver and spleen tissue of one-month-old male Sprague-Dawley rats. They verified the role of glucocorticoids by then treating with the glutocorticoid receptor antagonist mifepristone, which abrogated dexamethasone induction of TTP. Analyzing TTP gene transcription by dexamethasone, the researchers were able to determine that the effect of dexamethasone on TTP occurred at a primarily transcriptional level. They also showed that induction of TTP was critical for dexamethasone inhibition of the inflammatory cytokine tumor necrosis factor alpha (TNFα) mRNA expression post-transcriptionally.

Clinicians commonly prescribe glucocorticoids to treat immune and inflammatory diseases. Understanding this novel pathway may have wide-ranging clinical implications in the design of new glucocorticoids with a focus on transrepression-selective compounds.

Citation: Smoak K, Cidlowski JA. Glucocorticoids regulate tristetraprolin synthesis and posttranscriptionally regulate tumor necrosis factor alpha inflammatory signaling. *Mol Cell Biol* 26(23):9126-9135.

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Did You Know?

New Monthly Nanotechnology Seminar Series Begins

By Robin Mackar

On January 18, nearly 500 people attend the first NIEHS "Risk-e-Learning" monthly web seminar on "Nanotechnology – Applications and Implications for Superfund." The series addresses the increasing use of nanotechnology additives and products and the growing interest among scientists and concerned citizens in safety-related research on nanomaterials.

The debut session featured Nigel Walker, Ph.D., of the National Toxicology Program (NTP) and Nora Savage, Ph.D., of the EPA Office of Research and Development. Walker discussed both the progress and the challenges that confront environmental medicine and nanomaterials. Walker emphasized that all nanomaterials are not the same and make up a truly a diverse class of materials. The session covered definitions, forms and uses of nanotechnology and provided an overview of efforts underway by NIEHS, NTP and EPA to characterize the risks these materials may pose.

The NIEHS Superfund Basic Research Program (SBRP) is sponsoring the interactive web-based series as part of an ongoing collaboration with the EPA. Each monthly online seminar will highlight the potential of nanotechnology to support characterization and remediation of hazardous waste sites, as well as explore the potential risks of this new class of compounds.

SBRP Director William Suk, Ph.D., who was the moderator of the first event, was gratified by the response to the first seminar and anticipates even greater participation as the series continues. "Environmental experts, regulators and the general public are eager to learn as much as they can about what impact nanomaterials will have on their work and lives," he said. "We are in a unique position to provide the best information currently available."

Further information and the schedule for the monthly web seminar are available online. The Weekly Scientific Events e-mail messages will also include announcements of upcoming seminars.

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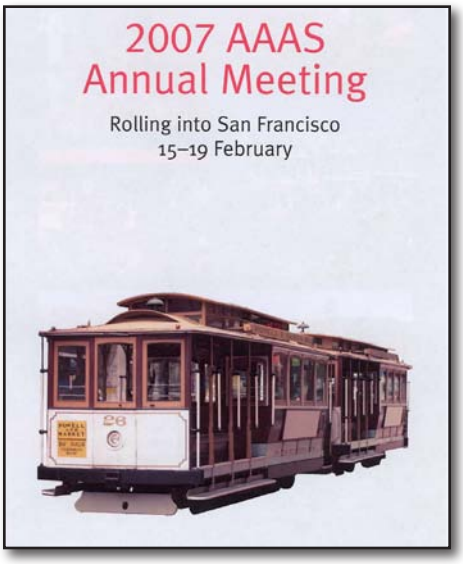
NIEHS Researchers to Lead AAAS Symposium

By Eddy Ball



On February 17, Health Science Administrator Jerry Heindel, Ph.D., and Laboratory of Molecular Toxicology Supervisory Biologist Retha Newbold will make presentations at the 2007 Annual Meeting of the American Association for the Advancement of Science (AAAS) in San Francisco. Heindel and Newbold will be featured speakers in the Obesity: Developmental Origins and Environmental Influences Symposium organized by Heindel.

Heindel, who works in the DERT Cellular, Organ and Systems Pathobiology Section, will speak on "Developmental Origins and Environmental Influences of Obesity: Clinical Relevance." Laboratory of Molecular Toxicology Investigator Newbold will deliver a presentation titled "Developmental Exposure to Environmental Estrogens is Associated with Obesity Later in Life."

Both presentations will explore the issue of the effects of endocrine disruptors on human health. Heindel was the organizer of the expert panel on bisphenol A, which was held in November in Chapel Hill. Newbold and another speaker at the symposium, Frederick vom Sall, Ph.D., also presented at the November expert panel. Scientists associated with the National Toxicology Program and several intramural labs at NIEHS are also involved in endocrine disruptor research.

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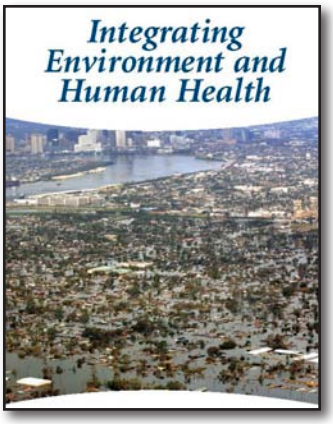
NIEHS at Integrating Environment and Human Health Conference

By Eddy Ball



NIEHS staff will travel to Washington, DC, to attend Integrating Environment and Human Health, the Seventh National Conference on Science, Policy and Environment on February 1 and 2. The National Council for Science and the Environment sponsors the event, in conjunction with the Environmental Protection Agency and the U. S. Geological Survey. NIEHS is supporting the conference as a patron.

The conference will feature lectures by leading national figures in the field and breakout sessions on Decision Making in the Real World, Guiding and Fostering Multi-disciplinary Research, Expanding Understanding: Information, Education and Communication, Avian Flu, and New Orleans and Katrina: Environment and Health Causes and Consequences.

Director Emeritus and Laboratory of Molecular Genetics Chief, Metastasis Group, Ken Olden, Ph.D., will attend. Other NIEHS staff at the conference include Program Analyst Beth Anderson, Biologist Barbara Burkhart, Ph.D., EHP Acting Editor-in-Chief James Burkhart, Ph.D., Contractor Daniel Cooper, Julia Gohlke, Ph.D., and EHP News Editor Kimberly Thigpen Tart.

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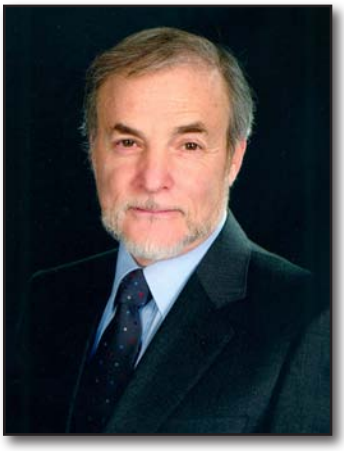
Upcoming Event — Distinguished Lecturer Stephen Baylin

By Eddy Ball



February Distinguished Lecturer Stephen Baylin (Photo courtesy of Johns Hopkins University)

Stephen B. Baylin, M.D., will deliver the next talk in the 2006-2007 NIEHS Distinguished Lecture Series at 11:00 AM on February 13 in Rodbell Auditorium. He will lecture on "Cancer: The Environment and the Epigenetic Interface."

Baylin is the Virginia and D.K. Ludwig Professor for Cancer Research at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University School of Medicine. According to the center's web site, his research has made significant contributions to the concept that epigenetically-mediated loss of gene function is a major player in the progression of human cancer. The work of the Baylin lab has highly translational connotations, which it pursues in close liaison with clinical activities in the Cancer Center. The focus of the Baylin laboratory is to understand the mechanisms underlying the appearance of the aberrant gene promoter hypermethylation in cancer and the identification of gene and molecular markers for cancer risk assessment, early diagnosis and prognostic monitoring of risk for recurrence.

Laboratory of Molecular Carcinogenesis Investigator Paul Wade, Ph.D., is sponsor of the lecture.

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Upcoming Event — UMBC President to Speak for Black History Month

By Eddy Ball

UMBC President Freeman Hrabowski (Photo courtesy UMBC Office of the President)

University of Maryland, Baltimore County (UMBC) President Freeman Hrabowski, Ph.D., will be the featured speaker at the NIEHS Black History Month Celebration on February 20 at 10:00 AM in Rodbell Auditorium. NIEHS Diversity Council and the Research Triangle Park Chapter of Blacks In Government are joint sponsors of the event.

In addition to being the chief executive of one of Maryland's honors universities and a scholar honored many times for his achievements, Hrabowski is a passionate advocate of quality science and math education, with special emphasis on minority participation and performance. He serves as a consultant to the National Science Foundation, the National Institutes of Health, the U.S. Department of Education, and universities and school systems nationally. He also sits on numerous corporate and civic boards, including the American Association of Colleges & Universities, Carnegie Institution of Washington, Marguerite Casey Foundation, McCormick & Company, Inc., and the University of Maryland Medical System.

Hrabowski has close links to NIEHS through the Meyerhoff Scholarship Program, which is based at UMBC. The university collaborates with NIEHS to broaden research experiences for students.

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Also Upcoming

- **February 2** in Rall F193, 10:00 – 11:00 — Seminar with Jin Zhong Li, D.V.M, Ph.D., speaking on "Applications of Virus Based Gene Delivery to Nervous System"

- **February 5** in Rodbell C, 10:00 – 11:00 — Carmen J. Williams, M.D., Ph.D., speaking on "Epithelial Membrane Protein-2 (EMP2) in Endometrial Function and Dysfunction"

- **February 8** in Rall F193, 10:30 – 11:30 — LPC/LMT Seminar Series with Linda S. Birnbaum, Ph.D., speaking on "Brominated Flame Retardants: What We Know and What We Don't"

- **February 13** in Rodbell, 11:00 – 12:30 — Distinguished Lecture Series with Stephen B. Baylin, M.D., speaking on "Cancer: The Environment and the Epigenetic Interface"

- **February 14** in Rall D350, 12:00 – 1:00 — LMG Seminar Series with Wataru Nakai speaking on "Double-strand Breaks to Chromosome Breaks"

- **February 15** in Rodbell C, 8:00 – 5:30 — National Advisory Environmental Health Sciences Council (NAEHSC) Meeting

- **February 15** Black History Month lunchtime talk at the Radisson Hotel — Irving Joyner, J.D., speaking on "From Slavery to Freedom in Durham. How Civil Rights Fueled Progress of Africans in the Americas: Past and Present

- **February 19** in Rall D350, 10:00 – 11:00 — LMG Seminar Series with Karen Vasquez, M.D., speaking on "Repair of Genome-destabilizing Lesions in Mammalian Cells"

- **February 20** in Rodbell B, 8:00 – 12:00 — Black History Month Program with Freeman Hrabowski, Ph.D.

- **February 27** in Rodbell, 9:00 – 3:00 — Black History Month Health Forum on Depression, speakers to be announced

- **February 28** in Rodbell, 8:30 – 4:30 — North Carolina Association for Biomedical Research Science Teacher's Workshop

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