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NIEHS Spotlight

Science Notebook

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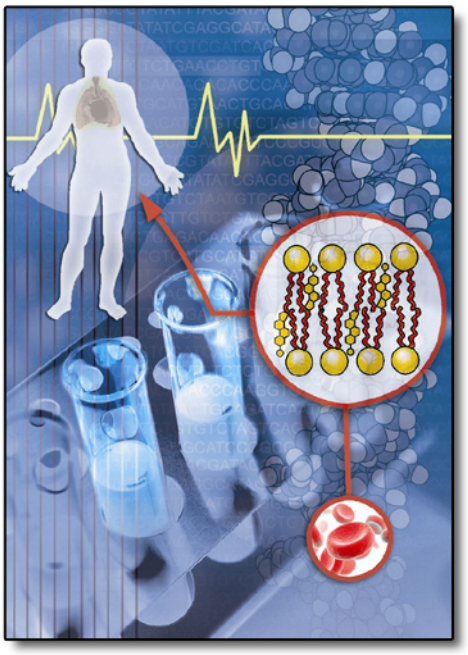
NIEHS Spotlight

NTP Retreat Considers Program's Directions

By Eddy Ball



The National Toxicology Program (NTP) held its two-day retreat at the North Carolina Biotechnology Center October 19-20. With some seventy scientists in attendance, the retreat offered the program an opportunity to evaluate its major initiatives, its roadmap and its vision in light of a flat budget and changing conditions. One purpose of the retreat was to gather as many staff together as possible and get them to talk about some of the major issues facing NTP. The retreat gave participants a chance to ask, "Where are we?" and "Where are we going?"

According to the organizing chair for the event, Center for the Evaluation of Risks to Human Reproduction Deputy Director Paul Foster, Ph.D., "This was a time for the members of the NTP to internalize all the information we've gotten from a series of workshops held over the past 18 months" and decide where the program needs to go in the future. Attendees heard reports on the pathology peer review process and the host susceptibility initiative that will evaluate known toxicants in multiple mouse species to tease out potential differences in genetic susceptibility. The group also considered developments in the process of selecting stocks and strains of test animals, how to utilize high throughput screening, how to evaluate tumors that occur as a result of endocrine system changes, and which new biomarkers will be most appropriate for future inclusion in future testing activities. Foster reported that the group made progress in several areas.

Foster pointed to an important consensus that emerged from the meeting. "NTP is planning to move toward more routine use of perinatal dosing. That means we'll expose animals beginning *in utero* in our cancer studies." This new emphasis on *in utero* exposure will establish the beginning point for NTP studies unless investigators can present good reasons for not performing perinatal exposures. The move answers the concerns of many researchers that perinatal exposure for many cancers, for example, may be critical in disease development.

One concern that ran throughout the discussions was process and how to make the program more effective and efficient as it moves into the 21st century. The pathology peer review process, for example, can be unusually time consuming. Other processes, such as nominations of chemicals for testing, have bottlenecks. "Bear in mind that when NTP does its carcinogen bioassays, they are recognized as the gold standard everywhere in the world, and so we don't want to throw the baby out with the bath water," Foster explained. On the other hand, Foster argued that there are places where NTP can compress the nomination-to-report process significantly.

As NTP approaches its thirtieth anniversary in 2008, members also wonder about identity and place. Interim Associate Director Allen Dearry stated that the retreat was not only a good start at addressing NTP's character and redefining its goals, but was also an excellent step forward in implementing many of the ideas and recommendations emerging from the past years' workshops. "It was especially pleasing and gratifying to see so much interest and enthusiasm in moving to make the NTP Roadmap a reality and in initiating a number of new directions," Dearry noted following the retreat.

As NTP considers its place in the larger NIH and DHHS scientific community, its members continue to work to safeguard public health from hazardous chemicals in food and the environment. With more than 80,000 chemicals registered for use in the U.S. and an estimated 2,000 more added each year, the program has its work cut out for it. The NTP retreat and the work to follow in its wake will help this important player in public health fulfill its mission to expand the scientific basis for making public health decisions on the potential toxicity of environmental agents.

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Environmental Justice, Community Participation Grantees Annual Meeting

By Eddy Ball

Rodbell Auditorium was filled to near capacity on October 26 as the Division of Extramural Research and Training (DERT) opened its annual meeting on Environmental Justice (EJ) and Community-Based Participatory Research (CBPR). Welcoming the researchers to NIEHS, DERT Director Anne Sassaman, Ph.D., commended their successful efforts to "build dialogue and build partnerships" as well as develop a "broader definition of what environmental science and environmental health are all about."

Schwartz outlined his vision for future environmental science research for EJ and CBPR grantees. (Photo courtesy of Steve McCaw)

Roy Fleming, Sc.D., National Institute for Occupational Safety and Health (NIOSH) director, Research Grants Programs, also welcomed the participants. He explained the process of translational research in EJ and CBPR projects, especially those funded in collaboration between NIOSH and NIEHS.

EJ Program Administrator Liam O'Fallon organized and moderated the two days of panel presentations and workshops. The purpose of the meeting was to highlight the many successes of the projects and to plan for the future. The diverse populations served in the project were reflected in the welcome statement in the meeting's abstract collection. The word "welcome" appeared in the eight languages represented in the projects: English, Navajo, Yupik, Lakota, Portuguese, Vietnamese, Spanish and Cape Verdean Kriolu.

The projects are unique in fostering and strengthening partnerships among researchers, community groups and health care providers to address environmental health issues facing communities. John Sullivan of the University of Texas Medical Branch in Galveston facilitated the keynote panel, which focused on "Environmental Justice in the Wake of Hurricanes Katrina and Rita." Speakers reported on post-disaster efforts in the Gulf Coast region (see the following story on the project "A Safe Way Back Home").

Other project sites discussed include agricultural fields with high levels of pesticide exposures in California, hog farms in North Carolina, urban environments in Harlem, Lowell, Mass., Chicago and Houston, and abandoned defense sites in Alaska. Among the populations served by the 19 NIEHS-funded projects are inner city Hispanics and African-Americans, Brazilian immigrants, indigenous populations, and Vietnamese and Cape Verdean poor and working poor. Issues ranged from nuclear waste and toxic metals to indoor air quality and asthma.

Grantee Gary Grant of the Tillery (N.C.) People's Clinic raised concerns about how EJ projects will fare with the institute's new emphasis on disease pathology. (Photo courtesy of Steve McCaw)

EJ and CPBR projects have produced hundreds of broad-based coalitions, publications, public health impacts and policy impacts, all of which influence the direction of public discourse and increase awareness of issues. The translational ends of this kind of research are realized most visibly when community groups adopt recommendations and government agencies on the local, state and federal level implement project recommendations into remediation/abatement efforts and regulatory guidelines.

The meeting culminated with NIEHS Director David A. Schwartz' presentation on "Mainstreaming Environmental Health Sciences" and a discussion of future funding opportunities and challenges. Referring to new directions for extramural research in the context of the Strategic Plan, Schwartz outlined ways that EJ and CBPR grantees can take advantage of new grant opportunities through the R01 process for funding their research efforts.

Some participants expressed concern that these community-based projects would be marginalized by the institute's new directions and the language used to describe the institute's new initiatives. Several felt that the movement away from specific EJ and CBPR requests for applications may affect future support from NIEHS.

Schwartz emphasized the institute's ongoing commitment to environmental justice and community-based research. "We're funding an enormous amount of research related to community-based problems," he explained. He then pointed to the Disease Investigation through Specialized Clinically Oriented Ventures in Environmental Research (DISCOVER) program with its emphasis on bringing together basic, clinical and population-based scientists. He said that DISCOVER represents one way NIEHS is incorporating community-based research into interdisciplinary research teams.

"I really do admire what you're doing…[and] what you've accomplished over the past five to ten years," Schwartz concluded. "And I look forward to working with you again."

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Environmental Justice Project Demonstrates How to Clean up New Orleans

By Eddy Ball

Presenters in "Environmental Justice in the Wake of Hurricanes Katrina and Rita" used their recent hurricane response efforts to highlight the specific ways that Environmental Justice/Community-Based Participatory Research grantees conduct translational research. An important factor in the success of these projects is forming working and funding partnerships to develop effective models for government agencies and community groups to implement.

Panelists included NIEHS Industrial Hygienist Sharon Beard of the Worker Education and Training Branch, Analytic Chemist and Environmental Consultant Wilma Subra and Bishop James Black of the Center for Environmental and Economic Justice in Biloxi, Miss. The fourth member of the panel, Labor Institute Associate Director and United Steel Workers (USW) Shop Steward Paul Renner, reported on "A Safe Way Back Home," a unique demonstration project in New Orleans.

The project set out to demonstrate cost-effective ways that could be applied city-wide to conduct a clean up and create opportunities for individuals and small businesses. What resulted, he said, was a model for government agencies to "create jobs for people, clean up that place and make it environmentally safe."

For residents of 8141 Aberdeen, A Safe Way Back Home meant a new yard where children can play without fear of exposure to arsenic-laced soil. Workers trained in hazardous material abatement removed the top four inches of sod. FEMA trucks later removed dirt and debris from the curbside. (Photo courtesy of United Steel Workers)

The environmental neighborhood clean up initiative and community outreach campaign Renner helped oversee was a joint effort of Dillard University's Deep South Center for Environmental Justice (DSCEJ) and the USW. The $35,000 project focused on removing tainted soil from residences in the 8100 block of Aberdeen Road in New Orleans.

Analysis of sediment samples taken by the US Environmental Protection Agency (EPA) from two properties at the project site showed that all but one sample contained levels of chemicals at a higher concentration than state or EPA guidelines. In some samples, arsenic levels were more than 40 times EPA guidelines. In one property, diesel range organics were twice the state levels, and high levels of polycyclic aromatic hydrocarbons were found at the other.

Over a four-day period in a one block area, project workers removed at least four inches of contaminated top soil from the yards of 27 homes. They then stacked the contaminated sod in the streets for removal by FEMA contractors and landscaped each lot with river sand and fresh soil. At the conclusion of the project, workers pressure-washed sidewalks, curbs and streets to remove contaminants.

College students on Spring Break, local volunteers and project members formed work crews that fanned throughout the square block on Aberdeen. NIEHS WETP funding trained and equipped the crews for safe and effective waste removal with hard-to-obtain respirators, helmets and protective gloves. (Photo courtesy of United Steel Workers)

Project funding sources included four USW employers and non-profit groups, such as the Ford Foundation and the National Resources Defense Council. NIEHS provided funds for Hazardous Waste Worker Training Programs and Minority Worker Training Programs as models for educating cleanup workers about how to identify, control and prevent potential health hazards. Volunteers came from groups throughout the U.S., many of them college students on Spring Break. Local groups and businesses donated the use of space and earth-moving services.

Training by the USW ensured the safety of volunteers. The program also offered small and disadvantaged businesses and contractors involved in demolition, debris removal, mold remediation and clean-up in the city of New Orleans the opportunity to obtain certification in hazardous materials remediation.

"A Safe Way Back Home" was a highly successful demonstration project that served, in the words of its architect, DSCEJ Director Beverly Wright, Ph.D., "as a catalyst for a series of activities that will attempt to reclaim the New Orleans East community." For her role in the project, Wright received the prestigious $120,000 National Robert Wood Johnson Gulf Coast Community Health Leadership Award. For Renner, the project was another effort in a career devoted to helping disenfranchised people achieve solidarity and justice.

NIEHS Worker Training Education Program (WETP)

In her panel presentation on October 26, NIEHS Industrial Hygienist Sharon Beard outlined some of the ways that NIEHS has helped displaced residents of the Gulf Coast in the wake of Katrina and Rita and met other training needs elsewhere since 1987. WETP has awarded Minority Training Program and Brownfields Program grants to a number of projects for meeting unanticipated training needs related to hazardous wastes and natural disasters, as well as helping minority workers and contractors become qualified in hazardous material abatement. Among WETP accomplishments are the following:

- Developing "gold standard" model training programs in conjunction with public health specialists and other experts to build participants' skills
- Funding 18 different non-profit organizations and universities, representing over 80 groups involved in training programs for workers engaged in hazardous materials response, emergency response, radiation abatement and, most recently, weapons of mass destruction response
- Creating national benchmarks for training and minimum criteria for health and safety training that became Appendix E of the Hazardous Waste Standards, 1910-120
- Awarding grants for training minority environmental and construction workers, preparing more than 6200 workers since 1995

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Fourth Annual Science Awards Day

By Eddy Ball

The NIEHS research community gathered in Rodbell on November 2 to recognize the outstanding achievements of its youngest members and to honor winners of the Early Award, Scientist of the Year and Mentor of the Year. Monitored by Special Assistant to the Scientific Director Joel Abramowitz, Ph.D., Science Awards Day is in its fourth year, and, for the first time, the steering committee invited winners of Summers of Discovery poster session back to participate.

NIEHS Director David A. Schwartz, M.D., delivered introductory remarks to attendees, emphasizing the importance of nurturing young investigators and recognizing their accomplishments. "This is a very important event for the institute," he said. "It recognizes the importance of the individual scientist here at NIEHS."

Event organizer Joel Abromowitz enjoyed remarks by Schwartz about the uncharacteristically formal attire worm by principal investigators on Science Awards Day. (Photo courtesy of Steve McCaw)

Early Award Winner Karen Adelman's enthusiasm for her work was obvious throughout her presentation. (Photo courtesy of Steve McCaw)

Scientific Director Lutz Birnbaumer, Ph.D., introduced Early Award Winner Karen L. Adelman, Ph.D., who presented her research "Stuck in the Starting Gates: Controlling Gene Expression by Regulating Early Transcription Elongation." Adelman and her colleagues have discovered previously unrecognized complexity in transcription patterns, especially among genes involved in response to environmental stimuli. These genes overlap interestingly with genes involved in immune response, genes which must react quickly to stimulus to protect the body. Some of the genes whose transcription patterns Adelman has elucidated are involved in HIV and the pathology of breast and upper gastrointestinal tract cancers, suggesting that her work may contribute to potential clinical applications.

With their colleagues and mentors in attendance, eight post-doctoral fellows gave fifteen-minute oral presentations each of studies on which they served as lead investigators. Two poster sessions took place mid-day, with a total of 73 poster abstracts on display accompanied by the post-doctoral lead researchers.

A panel of regional health scientists served as judges for the two scientist awards and poster awards. Along with selected NIEHS Fellows, DIR principal investigators and DIR staff scientists, the panel also judged platform presentations. The Board of Scientific Counselors chose the paper of the year among papers published in 2005, and the NIEHS Trainees Association selected the Mentor of the Year.

Scientist of the Year Ron Mason explained the simplicity and power of immuno-spin trapping. (Photo courtesy of Steve McCaw)

Visiting Fellow Mahua Ghosh-Ghosal of the Laboratory of Structural Biology described her research during the poster session. (Photo courtesy of Steve McCaw)

For the final presentation of the day, Schwartz introduced the winner of the Scientist of the Year Award, Research Chemist Ronald Mason, Ph.D., of the Laboratory of Pharmacology and Chemistry. Mason spoke on "Do It Yourself Detection of Protein and DNA Free Radicals in Organelles, Cells, and Tissues: A 30 Year Odyssey."

Mason has been involved in free radical research since the 1970s, when investigators first began detecting evidence of free radical formation related to human disease. Because free radicals are very unstable, detection was difficult and expensive, relying on highly sophisticated equipment, such as Electronic Spin Resonance, that required specially trained people to operate it. Mason's work developing an immuno-spin trapping methodology using standard laboratory platforms has opened free radical investigation to many more researchers. Using immuno-spin trapping, free radical investigation now can be performed with a much greater degree of sensitivity by virtually any laboratory scientist for a fraction of the cost of the previous methodology. The enhanced sensitivity has the further advantage of allowing researchers to use concentrations of hydrogen peroxide that are physiologically plausible.

2006 Science Day Award Winners

- *Mentor of the Year,* Senior Investigator David S. Miller, Ph.D., Laboratory of Pharmacology and Chemistry
- *Best Poster Presentation in Environmental Biology*, Saverio Gentile, Ph.D., Laboratory of Neurobiology, "SNP-dependent changes in protein kinase recognition sequences in ion channel proteins."
- *Best Poster Presentation in Environmental Diseases and Medicine*, Yong-Sik Kim, Ph.D., Laboratory of Respiratory Biology, "The crosstalk between the Krüppel-like zinc finger protein Blis2 and Wnt/2-catenin signaling."
- *Best Poster Presentation in Environmental Toxicology*, Wendy N. Jefferson, Ph.D., Laboratory of Molecular Toxicology, "Neonatal exposure to the endocrine disruptor genistein adversely affects fertilization rate and oocyte quality."
- *Best Oral Presentation*, Paige J. Adams, Ph.D., Laboratory of Neurobiology, "Role of NMDA receptors in action potential generation: Consequences on ERK activation and gene transcription."
- *Paper of the Year*, From the Laboratory of Signal Transduction, Lu NZ and Cidlowski JA 2005. Translational regulatory mechanisms generate N-terminal glucocorticoid receptor isoforms with unique transcriptional target genes. Mol Cell 18(3): 331-342.

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Intramural Scientist Named "Highly Cited Researcher"

By Eddy Ball

As a measure of the quality of research, the number of times an author's work is cited is arguably more important than the number papers and books he or she may have published. In recognition of the quality of one NIEHS scientist's work, the Institute for Scientific Information (ISI) has named Laboratory of Pharmacology and Chemistry Pharmacologist Joyce Goldstein, Ph.D., a "Highly Cited Researcher" in the category of pharmacology for her seminal work on polymorphisms in the human CYP2C enzymes.

Goldstein has been publishing in peer-reviewed publications since 1967, when she was completing her doctorate in pharmacology and biochemistry at the University of Texas Southwestern Medical School. ISI computed the frequency that other scientists cited her work on the basis of her publications in peer-reviewed journals, using a rolling 20-year period time period beginning in 1981 as the base for its calculations. ISI did not include citations of the book chapters she has also authored or consider her other professional achievements.

Highly Cited Author Joyce Goldstein. (Photo courtesy of Steve McCaw)

When Goldstein first learned of her selection, she did not completely appreciate its significance. However, as she began to explore the ISI Highlycited.com website, she started to realize that she was being recognized as one of the 250 most influential researchers in her field. "It's a nice atta-boy for me," she said. "And it's been interesting to see who else is highly cited and how many highly cited researchers other institutions have."

After her post-doctoral training at Emory University, Goldstein took a job the Communicable Disease Center in Atlanta. Two years later, her branch was transferred to the Environmental Protection Agency, where she worked for the next seven years. Goldstein joined NIEHS in 1977 as a group leader in the Systemic Toxicology Branch. In 1989, she joined the Human Metabolism section of the Laboratory of Biochemical Risk Analysis. For the past ten years, she has served as section head of Human Metabolism, Laboratory of Pharmacology and Chemistry.

"I've come a long way," Goldstein said of her career and the pride her parents felt about her accomplishments while they were living. "My father had an eighth-grade education, but my mother was set on her children going to college," she said. "I believe my father also saw the limitations that the lack of higher education imposed. He worked hard and saved to provide. I owe both of them a lot for the sacrifices they made to see that I had opportunities they didn't have for an education."

With the award, Goldstein joins the handful of NIEHS scientists named as ISI "Highly Cited Researcher." The group includes Scientific Director Lutz Birnbaumer, Ph.D., Chief, Laboratory of Structural Biology, Thomas Kunkel, Ph.D., and Laboratory of Signal Transduction Pharmacologist James Putney, Ph.D., all of whom won in the field of biology and biochemistry.

The ISI Highly Cited Researchers program began in 2000. It is the most recent in a series of projects at Thomson Scientific to recognize the contributions of the most influential authors in 21 scientific fields, half of them related in some way to the types of research conducted by NIEHS scientists and grantees. The awards are based solely upon the objective criterion of number of citations.

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St. Jude's Researcher Gives Falk Lecture

By Eddy Ball (with Robin Mackar)

On November 14, immunologist Doug Green, Ph.D., became the twenty-second distinguished researcher to present a lecture in the Hans L. Falk Memorial Lecture Series. Green's lecture was sponsored by Ben Van Houten, Ph.D., DERT Program Analysis Branch chief and Laboratory of Molecular Genetics investigator. Green holds the Peter C. Dougherty Endowed Chair of Immunology at St. Jude's Children's Research Hospital and chairs the hospital's Department of Immunology. Green spoke on "Apoptosis: The Paths of Perdition" to an audience of scientists that included Falk's widow and son.

Host Ben Van Houten (left) welcomed Falk Lecturer Doug Green to NIEHS (Photo courtesy of Steve McCaw)

As Green said in the lecture, apoptosis is "a matter of life and death," affecting every cell type and organ system of the body. Apoptosis is the process that protects an organism from the spontaneous cell transformation that occurs in cancer. Although many aspects of the process are still not completely understood, productive research in the past decade has provided insights into strategies for blocking pathological cell loss or for killing unwanted cells.

Green's major research effort is to unravel the "dance of death" that is a normal stage of cell growth and to understand how apoptosis may be triggered to kill tumor cells without damaging healthy ones. Green has worked to elucidate the processes by which specialized "cutter" enzymes known as caspases orchestrate the process. Under normal conditions, specialized changes in the permeability of the mitochondrial outer membrane trigger the diffusion of death promoting proteins such as cytochrome c. Stimulated by these proteins, "initiator" carpases activate the "executioner" enzymes necessary for engaging the apoptotic cascade.

Green delivered on his promise to entertain his audience and make the intricacies of apoptosis fascinating even for the uninitiated. (Photo courtesy of Steve McCaw)

Green and his colleagues have explored signaling pathways in an effort to find ways to induce cytochrome c release and activate what he calls the "gates of death." In this way, he hopes to circumvent the defenses that allow tumor cells to defy the cell's numerous stressor-generated signals, including DNA damage and growth factor withdrawal, that should stimulate apoptosis, whether carpase-dependent or independent.

In many human cancers, tumors also develop resistance to chemotherapy. To discover where the normal progression of cell death for tumors is blocked, Green has examined a group of proteins, specifically the BCL-2 family, that serve as anti-apoptotic proteins, inhibiting the activation of the proteins essential for initiating the apoptotic cascade. Looking at promising

developments emerging from research into the apoptotic signaling pathways, Green pointed to BCL-2 antagonists that may be able to strip away the rogue cell's last defenses and target tumor cells for death.

Green is a prolific author and tireless researcher who serves on the editorial boards of nine scientific journals. With over 350 peer-reviewed articles to his credit, Green publishes an average of 15 studies per year and reviews approximately three studies for every one he publishes. He is among the 20 most highly cited scientific researchers in the world and a recipient of a National Institute of General Medical Sciences Merit Award.

The Hans L. Falk Memorial Lecture Series honors the contributions of the chemical carcinogenesis researcher who served NIEHS as Associate Director for Laboratory Research and Associate Director for Health Hazard Assessment. Falk was an NIEHS pioneer, arriving at the institute in 1967, shortly after its founding. He is credited with helping to establish the spirit of freedom of scientific inquiry and the pursuit of excellence in science that the lecture series celebrates.

Mrs. Falk and son Steven were honored guests at the lecture. (Photo courtesy of Steve McCaw)

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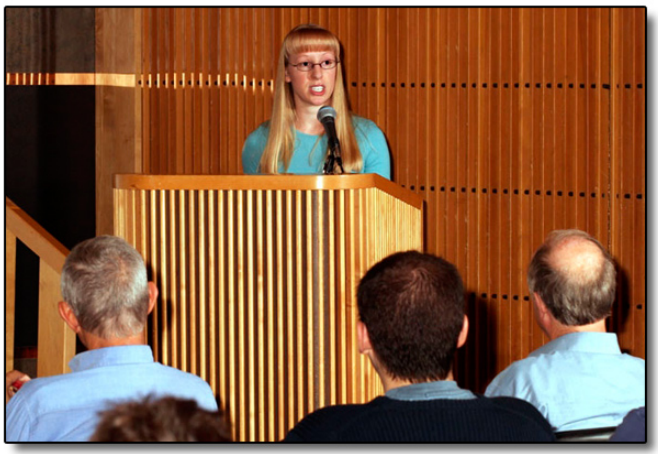
LMG Speaker Peter Burgers on DNA Clamps

By Eddy Ball

An enthusiastic audience of research fellows gathered in Rodbell on October 30 to hear Peter M. J. Burgers, Ph.D., deliver the second talk in the Laboratory of Molecular Genetics (LMG) Special Seminars Series. Hosted by LMG Fellow Stephanie Nick McElhinny, Ph.D., the professor of Biochemistry and Biophysics at Washington University School of Medicine gave a talk titled "When Good DNA Turns Bad: Clamps Slide to the Rescue."



Host Stephanie Nick McElhinny introduced the speaker. (Photo courtesy of Steve McCaw)

Burgers presented the latest results in his research group's investigations into the mechanisms of nuclear DNA replication and repair. The stability of an organism depends on its ability to maintain its DNA genome with a high degree of fidelity against the many accidental lesions that occur continually in DNA. DNA is subjected to stress and damage from heat shock, ultraviolet rays in sunlight, environmental exposures and metabolic processes. If an organism does not effectively replicate and repair DNA, cell mutation can occur with damaging and even life-threatening consequences.

Despite the thousands of random changes and "nicks" in DNA that occur daily, the repair process is so effective that only a few stable changes in DNA survive each year. Under normal conditions, a healthy organism is capable of quickly mounting emergency responses to severe DNA damage by synthesizing repair enzymes.

Burgers' talk focused on the role of two specialized DNA clamps in yeast that are associated with DNA repair. These clamps are donut-like protein assemblies that encircle double-stranded DNA and form organizing and stabilizing centers for enzymes that function in DNA metabolism. Burgers' laboratory has studied the proteins that participate with them in the repair process.

At several points in the otherwise serious lecture, Burgers shared humorous stories about his work. (Photo courtesy of Steve McCaw)

The first clamp Burgers discussed is involved in repairing damage at stalled replication forks in a process known as translesion DNA synthesis (TLS). His lab and others have identified a protein, Rev1, that interacts with ubiquinated proliferating cell nuclear antigen (PCNA) in order to initiate the TLS repair process. Studies have found that in vivo mutants in Rev1 interfere with TLS repair, indicating that Rev1 is essential for initiating the repair process.

The second clamp, the yeast PCNA-like checkpoint clamp, functions to halt the cell cycle in response to DNA damage. This interruption allows the organism to complete needed repairs prior to continuing the cell cycle to inhibit mutagenic development. Burgers' research team determined that a protein kinase, Mec1, forms a complex with the checkpoint clamp. Without the formation of the complex, necessary phosphorylation of downstream targets cannot take place, and the cell cycle will progress without repairs being made.

Understanding the clamp and clamp loading mechanisms in repair of DNA may ultimately offer insights into maintaining or restoring replication-competent complexes. This process is well conserved, and studies of DNA repair homologs in yeast and other lower organisms provide insight into the process in human cells.

Among the many honors he has received in the course of a career spanning 30 years, Burgers has been named an American Cancer Society Fellow and a Searle Scholarship Fellow. He has served of the editorial board of the Journal of Biological Chemistry, as well as a member of several NIH study sections. Burgers has contributed over 100 peer-reviewed articles to the medical literature and is the author of books and chapters on various aspects of biochemistry and biophysics.

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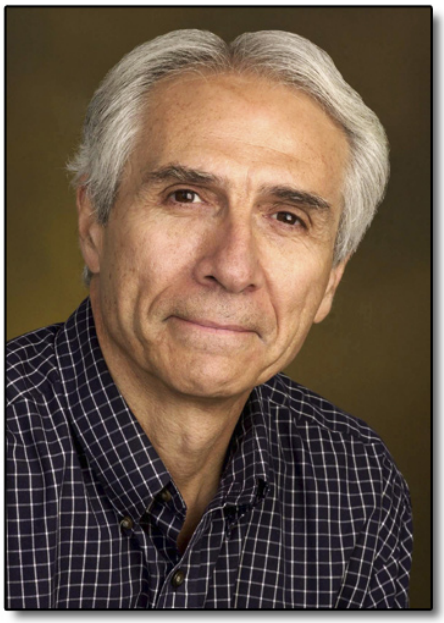
NTP Scientists Help New Treatment Enter Clinical Trials

By Eddy Ball

In a study published in the November issue of *Human Gene Therapy*, National Toxicology Program Chemist Richard Irwin, Ph.D., and Biologist Molly Vallant collaborated in a detailed toxicity and biodistribution analysis that has moved a novel gene transfer treatment protocol closer to clinical trial. In earlier studies, the protocol demonstrated promise for reducing side effects from radiation therapy for head and neck cancer.

As part of the pre-clinical approval process needed to progress to phases1 and 2 of human clinical studies, the Food and Drug Administration (FDA) required scientists from the National Institute of Dental and Craniofacial Research (NIDCR) to submit animal toxicity studies on the protocol. To get the data and

exhaustive analysis needed, researchers from NIDCR and BioReliance Invitrogen Bioservices partnered with experts at NTP to produce a "gold standard" study using Good Laboratory Practices.



NTP Chemist Richard Irwin
(Photo courtesy of Steve McCaw)

Approximately 40,000 patients are diagnosed with head and neck cancers in the United States each year. While survival rates have improved dramatically, the treatment causes severe damage to the fluid-secreting portion, or acinar cells, of the salivary glands that are within the field of radiation. Without enough saliva to lubricate and cleanse the teeth, mouth and throat, patients can experience dry mouth, damage to upper gastrointestinal tract tissues, tooth cavities, inflammation of mucus membranes in the mouth and frequent infections.

People also can have difficultly swallowing, speaking or tasting food, sometimes leading to a significant loss of appetite, considerable discomfort and a marked decline in quality of life. At the present time, there is no approved corrective treatment for the condition, known as radiation-induced salivary hypofunction.

Although radiation destroys the fluid-producing acinar cells, the ductal cells, which do not produce saliva, are usually not damaged. This observation led NIDCR Chief, Gene Therapy and Therapeutics Branch Bruce Baum, D.M.D., Ph.D., to collaborate in studies of salivary gland repair with then Johns Hopkins University Professor of Medicine Peter Agre, M.D. Agre discovered the water transport protein aquaporin in 1991 and was awarded the Nobel Prize in Chemistry in 2003 for his work.

NTP Biologist Molly Vallant
(Photo courtesy of Steve McCaw)

The scientists hypothesized that an effective treatment could be developed using a recombinant adenoviral vector, similar to a cold virus, to transfer the gene for human aquaporin-1, which forms pores in cell membranes, to ductal cells, turning them into fluid producers. In a series of experiments with radiated animals, including rats, miniature pigs and non-human primates, the investigators found that treatment resulted in a dose-dependent increase in salivary flow to 80 percent of normal, a two to three fold increase over post-radiation levels.

Irwin, Vallant and colleagues conducted detailed and careful studies of vector safety and biodistribution of the vector beyond the oral cavity. Animals were housed individually, treated humanely and anesthetized in accordance with the guidelines during vector administration and follow-up.

Researchers monitored the health of 200 adult male and female rats, divided into four experimental groups per gender, over a 92-day period. Animals in the test groups received injections of the virus containing the gene for aquaporin-1 into the submandibular duct. For toxicity determination purposes, the treatment dose was approximately ten times the corresponding lowest and highest doses proposed for clinical study. Researchers collected saliva, blood and salivary glands from five animals in each staggered start group 48 hours after vector administration.

Researchers observed no clinical or gross pathological signs of adverse toxicological effects in animals after gene transfer. There were no treatment-associated losses of animals. Animals in all groups continued to thrive after treatment, with normal patterns of weight gain and food and water consumption. Except for local,

dose-dependent inflammatory changes in the targeted gland, animals showed no severe or permanent damage to the salivary gland and limited vector distribution elsewhere in the body. Despite some gender differences in response to treatment, clinical chemistry indicators of major organ function were normal for all animals.

Citation: Zheng C, Goldsmith CM, Mineshiba F, Chiorini JA, Kerr A, Wenk ML, Vallant M, Irwin RD, Baum BJ. 2006. Toxicity and biodistribution of a first-generation recombinant adenoviral vector, encoding aquaporin-1, after retroductal delivery to a single rat submandibular gland. Hum Gene Ther 17:1122-1133.

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NIEHS Researchers Produce Reference Work on Lymphoid Organs

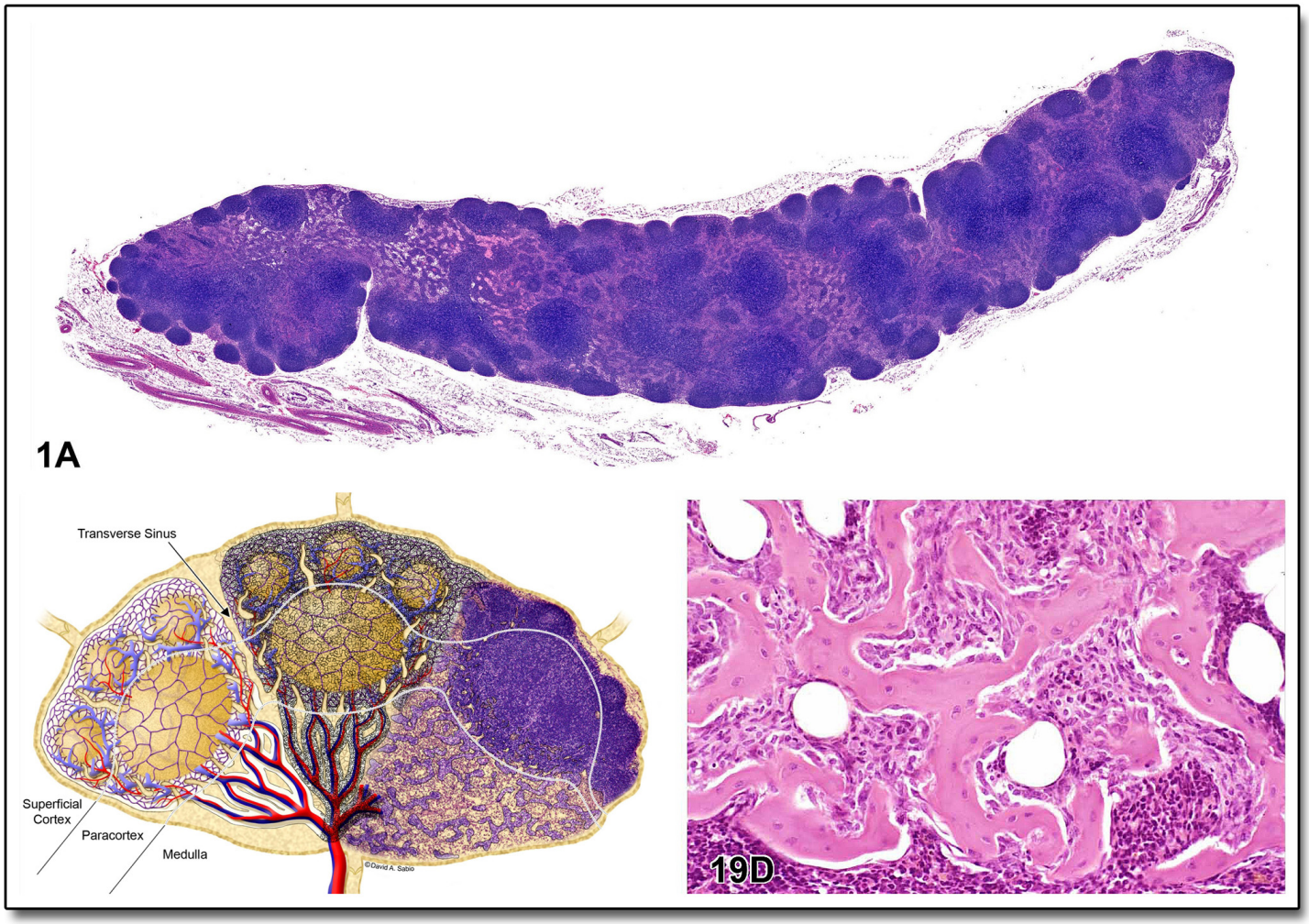
By Eddy Ball

A September special issue of the journal *Toxicologic Pathology* (34.5) holds a unique appeal for NIEHS researchers and provides a valuable reference source for toxicological studies. With its focus on histomorphologic evaluation of lymphoid organs, the issue features over 280 pages of commentary and photomicrographs, as well as a CD with 900 high-quality full-color photomicrographs, most of them from the National Toxicology Program archives at NIEHS.

Under the direction of guest editor and Laboratory of Experimental Pathology (LEP) Senior Scientist Robert Maronpot, D.V.M., the issue presents an illustrated review of the normal structure and pathology of the lymphoid system. This issue was a response to the 2005 Society of Toxicologic Pathology call for a guide to the pathological examination of lymphoid tissues as necessary and pivotal first steps in the assessment of new drugs for immunotoxic potential prior to approval by the Food and Drug Administration. The monograph is also relevant for the histopathological assessment of immunotoxic potential following exposure to environmental agents.

Most of the contributors to the issue are or have been affiliated with the institute. Within the issue, peer-reviewed papers discuss normal structure, function, pathology and enhanced histopathology for lymph nodes, thymus, bone marrow, spleen and mucosa-associated lymphoid tissues. Maronpot wrote the issue overview, "A Monograph on Histomorphologic Evaluation of Lymphoid Organs" and an introduction to "Enhanced Histopathology of Lympoid Tissues." LEP Veterinary Medical Officer Greg Travlos, D.V.M., contributed two papers on bone marrow. The issue also includes a paper on the immunohistochemistry of lymphoid organs and five papers by LEP Pathology Staff Scientist Susan Elmore, D.V.M., dealing with enhanced histopathology.

Although each article features color slides, the majority of the printed slides are reproduced in gray scale. The full-color images, most from hematoxylin and eosin-stained slides, are available on the CD that accompanies the issue and are of suitable resolution for teaching purposes. Individual purchasers may order this important reference work on-line for $25.



Representative examples of figures from the Toxicologic Pathology special issue "Monograph on Histomorphologic Evaluation of Lymphoid Organs." The top figure is a longitudinal histologic section of a normal mesenteric lymph node, showing the irregular and complex structure. At lower left is a diagrammatical of the complex internal structure of a normal lymph node. The lower right photomicrograph shows a histologic section of a bone marrow lesion in which the marrow spaces are replaced by proliferating bony and connective tissue. (Photomicrographs courtesy of Robert Maronpot)

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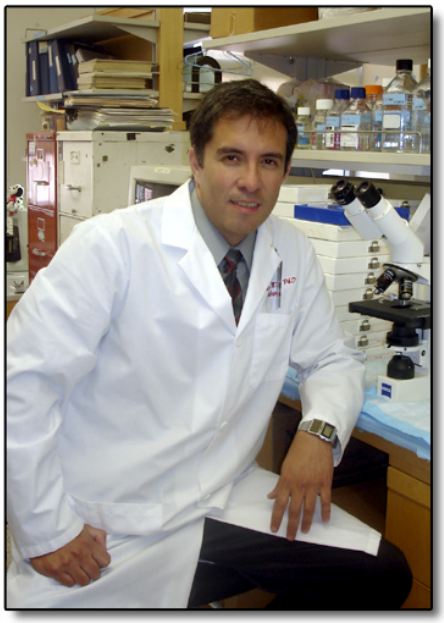
Extramural Researcher Shines at American Heart Association Meeting

By Eddy Ball

NIEHS-funded research by Jesus Araujo, M.D., Ph.D., received a Basic Science Research Award at the annual American Heart Association Scientific Sessions poster competition held November 12 – 15 in Chicago. Araujo is a cardiologist and assistant professor of medicine at the David Geffen School of Medicine at the University of California at Los Angeles. He was co-investigator for the study "Ambient Ultrafine Particulate Matter Enhances Atherosclerosis in apoE Null Animals."

According to DERT Cellular, Organ and Systems Pathobiology Branch Chief Pat Mastin, Ph.D., the research is important for its exploration of the contribution of exposure to air pollution, especially particulate matter (PM) air pollution, to cardiovascular disease. For the last 10 to 15 years, there has been growing epidemiologic evidence of an association between cardiovascular disease and PM, which is measured in microns or

micrometers. One micrometer is one millionth of a meter — about 75 times smaller than the width of a human hair. These tiny particles primarily come from motor vehicle exhaust, power plant emissions and other operations that involve the burning of fossil fuels. Araujo's award-winning study added significant evidence to support the hypothesis that increased exposure to PM in polluted air increases risk of atherosclerosis and may be especially harmful when combined with additional risk factors.



Award Winner Jesus Araujo
(Photo courtesy of Jesus Araujo)

Araujo's team examined the differences in the area of lesions in the ascending aorta of 62 apoE-null male mice. The investigators hypothesized that inhaled PM would act synergistically with known pro-atherogenic (cardiovascular disease promoting) stimuli and mediators. They predicted that PM, together with pro-atherogenic stimulators and mediators, would lead to a significant increase in the area of lesions due to increased oxidative stress. The team also expected that inhaled smaller particles would have a greater pro-inflammatory effect than larger ones. Test groups included non-exposed (NE) mice, animals breathing filtered air (FA), mice exposed to fine particulate matter (FP), less than 2.5 micrometers in diameter, and mice exposed to ultrafine particles (UFP), measuring less than 0.18 micrometer in diameter.

As predicted, the mice exposed to UFP over a 75-hour period developed significantly larger atherosclerotic lesions than the other groups. The area of the UFP mice lesions was nearly twice that of NE mice, over 50% greater than FA mice and 25% greater than FP mice. An in vitro analysis of human microvascular endothelial cell line confirmed that diesel exhaust UFP synergized with an oxidized LDL (the "bad" cholesterol) pro-atherogenic mediator to promote lesion development in the vascular wall. The exposure also led to the up-regulation of a large number of genes.

Araujo earned a M.Sc. degree in Immunology at the Venezuelan Institute for Scientific Research, an M.D. degree Magna Cum Laude at the Central University of Venezuela and a Ph.D. in Molecular Biology at UCLA. He completed internal medicine residency training at Beth Israel Medical Center, Albert Einstein College of Medicine in New York and a cardiology fellowship at UCLA Medical Center in Los Angeles. His research interests have focused on identifying cytoprotective genes relevant in vascular inflammatory processes such as atherosclerosis and cardiac allograft transplantation and, more recently, on dissecting the mechanisms on how air particulate matter exposure promotes atherosclerosis and ischemic heart disease. He is particularly interested in identifying prominent gene-environment links of relevance in cardiovascular pathology.

A grant from NIEHS through a joint NIEHS-EPA program, "The Role of Air Pollutants in Cardiovascular Disease," supported Araujo's research. Grantee Andre Nel, M.B.Ch.B., Ph.D., was principal investigator of the study. Nel is a practicing allergist/immunologist at UCLA and director of the Cellular Immunology Activation Laboratory in the Johnson Cancer Center at UCLA.

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NIEHS Scientists at Fall GEMS Meeting

By Eddy Ball

On October 26, the Genetics and Environmental Mutagenesis Society (GEMS) held its 24th Annual Fall Meeting on "Oxidative Stress and Damage" at the UNC Friday Center in Chapel Hill. The meeting was organized and facilitated by President-Elect Greg Stuart, Ph.D., a special volunteer with the NIEHS Laboratory of Molecular Genetics (LMG). The event featured invited platform speakers, as well as oral and poster presentations by three post-doctoral fellows affiliated with NIEHS.

GEMS President-Elect Greg Stuart (Photo courtesy of Steve McCaw)

At NIEHS, Stuart works in the Mitochondrial Replication Group with LMG Director William Copeland, Ph.D. He is supported by a National Research Council Research Associateship Award from the National Academies. Stuart's specialty at NIEHS is yeast genetics, the study of mutations synonymous with those in the human mitochondrial DNA polymerase gene, DNA polymerase gamma, that are associated with human neurological diseases. Stuart served on the GEMS Board of Directors as a councilor for three years prior to assuming his current position in 2005. He will serve as president through 2007.

At this year's fall meeting, Laboratory of Pharmacology and Chemistry (LPC) Fellow Dario Ramirez, Ph.D., participated in oral presentations with a talk titled "Immuno-spin Trapping of Oxidatively Generated Damage to the Genome." Ramirez' presentation grew out of his work with LPC Research Chemist Ronald Mason, the 2006 NIEHS Scientist of the Year. Ramirez was principal investigator on a study, "Immuno-spin Trapping of DNA Radicals," published in *Nature Methods* (2006, 3:123-127) and co-authored with Mason and LPC Fellow Sandra E. Gomez-Mejiba, Ph.D. Ramirez was the winner of the Best Talk/Travel Award in the post-doctoral category and was offered a one-year position on the board as a student representative. LMG Fellow D. Wade Lehmann, Ph.D., also presented a talk at the session titled "Aroclor Derived Oxidative Damage in the Bivalve *Corbicula fluminea*."

Best Post-Doctoral Poster Winner Mercedes Arana (Photo courtesy of Steve McCaw)

The meeting also featured a poster session. NIEHS scientist Mercedes Arana, Ph.D., LMG post-doctoral fellow, won the meeting's award for Best Post-Doctoral Poster. She was principal investigator in the study "A Unique Error Signature for Human DNA Polymerase ν" with co-authors LMG Fellow Miguel Garcia-Diaz, Ph.D., and LSB Chief Thomas A. Kunkel, Ph.D.

In addition to Stuart, five other NIEHS scientists serve on the GEMS Board of Directors. Gloria Jahnke, Ph.D., is secretary, and Janice Allen, Ph.D., is a 2005-2007 councilor. Biologists Rose Anne McGee, Dan Shaughnessy and Cindy Innes of the Laboratory of Molecular Toxicology are 2006-2008 councilors.

Founded in 1982, GEMS is a regionally active group of scientists, toxicologists, and others sharing a common interest in genetics and the environment. GEMS holds two scientific meetings annually with mutagenesis themes, such as the biological effects of toxicants on the environment or human health. The organization maintains a web page and blog for members and other interested scientists. "A long-standing and ongoing goal of GEMS," Stuart said, "is to actively encourage involvement at the meetings – and in science generally – by minority groups, women in science, and handicapped or other historically under-represented groups." GEMS promotes the participation of students by reducing their fees to $5.00 for membership and $10.00 for meeting registration, thus encouraging them to become involved in professional development early in their careers.

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Best Talk/Travel Award Winner Dario Ramirez (Photo courtesy of Steve McCaw)

DERT Papers of the Month

By Jerry Phelps

Aldose Reductase Inhibition Fights Sepsis

Sepsis is characterized by an overreaction of the immune system in response to a severe bacterial infection. Death usually occurs from heart or other major organ failure. The incidence of sepsis is on the rise; a study conducted by the Centers for Disease Control and Prevention found that the number of cases has nearly tripled in the past couple of decades — from 82.7 cases/100,000 Americans in 1979 to 240.4 cases/100,000 in 2000. Much of the reason for this dramatic increase is attributed to antibiotic-resistant bacteria, caused by the overuse of antibiotics, and conditions resulting in a weakened immune system.

Now NIEHS-supported researchers at the University of Texas Medical Branch report that by blocking the activity of the enzyme aldose reductase in laboratory mice, they can prevent the development of sepsis and the resulting heart failure brought on from endotoxin exposure. The researchers blocked aldose reductase activity either through administration of sorbinil or small interfering RNA. Endotoxin administration caused large increases in serum and cardiac cytokines; this response was suppressed when aldose reductase activity was inhibited. Aldose reductase inhibition increased survival in mice following lethal doses of endotoxin.

Previous work by this team has shown that blocking aldose reductase reduced the inflammation-driven processes in colorectal cancer and diabetes. A compound very similar to sorbinil is now undergoing phase III clinical trials for use in diabetes.

Citation: Ramana KV, Willis MS, White MD, Horton JW, DiMaio JM, Srivastava D, Bhatnagar A, Srivastava SK. 2006. Endotoxin-induced cardiomyopathy and systemic inflammation in mice is prevented by aldose reductase inhibition. Circulation 114(17):1838-46.

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Mutation Causes Some Cases of Brittle Bone Disease

Osteogenesis imperfecta (OI), also known as brittle bone disease, is a group of genetic bone disorders resulting in frequent fractures. A newly identified gene mutation helps explain a subset of cases of OI whose origin had until now remained mysterious. Brendan Lee at the Baylor College of Medicine and the Howard Hughes Medical Institute identified the mutation, which is responsible for up to 15 percent of OI cases. The mutation prevents collagen proteins from being properly modified after they are produced.

Using transgenic mice, Lee and his colleagues discovered that cartilage-associated protein (CRTAP) interacts with the enzyme responsible for the hydroxylation of the collagen protein. The mutation they discovered in CRTAP prevents this interaction and thus, prevents the protein modification resulting in damaged collagen and poor bone formation. The researchers reasoned that the same mutation might cause OI in humans. They focused on two families with a recessive form of OI that other researchers had mapped to the same chromosomal region containing the CRTAP gene. The research team found that a partial loss of CRTAP function caused OI and that a complete loss caused an even more severe form of the disease.

These findings could have important diagnostic implications. Until now, the only known genetic cause of OI was a structural mutation in type I collagen. According to Lee, this finding "adds a new dimension in terms of DNA testing." It also may also offer clues to the causes of connective tissue diseases that affect other parts of the body and gives insight into the basic mechanism of collagen formation.

Citation: Morello R, Bertin TK, Chen Y, Hicks J, Tonachini L, Monticone M, Castagnola P, Rauch F, Glorieux FH, Vranka J, Bachinger HP, Pace JM, Schwarze U, Byers PH, Weis M, Fernandes RJ, Eyre DR, Yao Z, Boyce BF, Lee B. 2006. CRTAP is required for prolyl 3-hydroxylation and mutations cause recessive osteogenesis imperfecta. Cell 127(2):291-304.

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Link Between DNA Repair and DNA Remodeling Proteins

Two proteins involved in chromatin remodeling interact with nucleotide excision repair damage-recognition proteins to play a key role in enabling cells to repair DNA damage, according to a new study by NIEHS-grantee Michael Smerdon and colleagues at Washington State University. Their paper, published in *Nature Structural and Molecular Biology* was named "Article of the Month."

The researchers exposed yeast cells to UV radiation to cause DNA damage and then studied the actions of several DNA-associated proteins including eleven proteins in a complex called SWI/SNF. SWI/SNF changes the shape and arrangement of DNA with its associated structural proteins. They found that in yeast cells undergoing high rates of DNA repair, SWI/SNF is physically attached to two key proteins involved in recognizing DNA damage — Rad4 and Rad23. In yeast cells with the SWI/SNF complex knocked out, the cells lost the ability to remodel DNA and to repair DNA damage.

Each cell in the human body sustains thousands of DNA lesions each day as a result of normal metabolic activity, regardless of lifestyle choices such as smoking, UV exposure and diet. Smerdon and his group are continuing their work in human cells containing a SWI/SNF complex that appears to function similarly to the yeast complex. Smerdon is a Method to Extend Research In Time (MERIT) grant recipient from NIEHS; a prestigious grant award given to very few NIEHS grantees.

Citation: Gong F, Fahy D, Smerdon MJ. 2006. Rad4-Rad23 interaction with SWI/SNF links ATP-dependent chromatin remodeling with nucleotide excision repair. Nat Struct Mol Biol 13(10):902-7.

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Subpollen Particles from Ragweed Pollen Contain Allegenic Proteins and Oxidases

Fragments of pollen grains, called subpollen particles (SPPs), are capable of reaching the lower regions of the lung and causing clinical symptoms associated with seasonal asthma, according to new research from NIEHS-supported researchers at the University of Texas Medical Branch in Galveston. How pollen allergens contribute to inflammation in the lower airways has been puzzling to researchers since only few pollen grains can reach the lower respiratory tract due to their size.

The researchers found that ragweed pollen grains release SPPs in the range of 0.5 to 4.5 microns in size. They determined that the SPPs contained allergenic proteins and possessed NADH or NADPH oxidase activity. Exposure of cultured cells to SPPs caused significant increases in the generation of reactive oxygen species and induced allergenic airway inflammation in laboratory mice. Pretreatment of the SPPs with NADH and NADPH oxidase inhibitors reduced their ability to increase reactive oxygen species in the airway epithelial cells and subsequently reduced airway inflammation.

These findings represent the first report showing allergenic proteins and oxidase activity by SPPs of respirable size produced by plants. The oxidase activity and the allergenic proteins work together to cause the development of severe allergic inflammation. The study provides insight into the role of SPPs in seasonal asthma and suggests that inhibitors of SPP oxidases may be useful therapeutic agents in reducing or preventing oxidative damage and inflammation.

Citation: Bacsi A, Choudhury BK, Dharajiya N, Sur S, Boldogh I. 2006. Subpollen particles: carriers of allergenic proteins and oxidases. J Allergy Clin Immunol 118(4):844-850.

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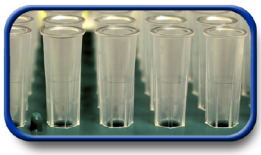

DIR Papers of the Month

By Eddy Ball

Network Analysis in Toxicology Studies

An NIEHS-funded research team has demonstrated the utility of systematic statistical analysis of microarray data for identifying differences between gene expression levels and patterns in high and low doses of acetaminophen. The team included investigators from the Laboratory of Molecular Toxicology and the Environmental Toxicology Program working in collaboration with Japanese researchers.

The team investigated gene interaction networks of 17 genes from livers of rats orally exposed to 50, 150 and 1500 mg/kg acetaminophen at 6, 24 and 48 hours after exposure. Using a variety of statistical and bioinformatics approaches, the researchers clustered nine dose-time observation points. Their networks related genes associated with oxidative stress to genes associated with apoptosis and demonstrate markedly different networks for the two lowest doses relative to the highest dose.

The results of this study indicate that gene interaction network analysis may prove useful for the development of biomarkers and assessing chemical toxicity. The gene interaction network/clustering approaches demonstrated

in this study can address questions of dose-dependent toxic responses seen in pharmaceutical applications and answer them in a scientifically rigorous manner.

Citation: Toyoshiba H, Sone H, Yamanaka T, Parham FM, Irwin RD, Boorman GA, Portier CJ. 2006. Gene interaction network analysis suggests differences between high and low doses of acetaminophen. Toxicol Appl Pharmacol 215(3):306-316.

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P-glycoprotein Up-regulation/Reduced Penetration of Therapeutic Drugs into CNS

Researchers from the NIEHS Laboratory of Pharmacology and Chemistry, in collaboration with UNC pharmacologists, have demonstrated the role of a nuclear receptor, the human pregnane-X receptor (hPXR), in altering the efficacy of a CNS-acting drug. The NIEHS-funded study showed that up-regulation of the blood-brain barrier transport protein P-glycoprotein by rifampin, an antibiotic and hPXR ligand, reduced the analgesic effects of methadone.

The experiments were performed *in vivo* and *in vitro* using male CB6F1 wild type mice and CB6F1 transgenic mice expressing hPXR. Researchers determined that pretreatment with rifampin reduced the pain-relieving effects of methadone in test animals by 70%, even though blood levels of the CNS-acting drug in test animals were similar to levels in controls not given the antibiotic.

Since the transgenic mice exhibited plasma rifampin levels identical to those found in patients, the findings suggest that hPXR-based changes in selective barrier function are likely to be widespread in the human population and may affect drug efficacy and safety. Blood-brain barrier P-glycoprotein is a major impediment to pharmacotherapy for a number of CNS diseases, including brain cancer and epilepsy. Alterations in transporter activity may underlie the multi-drug resistance seen in 30 % of epilepsy patients as well as patient-to-patient variability in response to CNS-acting drugs.

Citation: Bauer B, Yang X, Hartz AM, Olson ER, Zhao R, Kalvass JC, Pollack GM, Miller DS. 2006. *In vivo* activation of human pregnane X receptor tightens the blood-brain barrier to methadone through P-glycoprotein up-regulation. Mol Pharmacol 70(4):1212-1219.

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COX-1 Effects on Airway Responsiveness and Allergic Inflammation

In an NIEHS-funded study, a team of intramural researchers has demonstrated beneficial effects of constitutive over-expression of cyclooxygenase-1 (COX-1) on murine airway responsiveness to cholinergic stimulation — but not the anticipated beneficial effects on inflammatory and functional responses of the lung to an allergic stimulus.

Researchers used transgenic mice that over-expressed human COX-1 to study the roles of COX and COX-derived prostanoids in the lung under normal and inflammatory conditions. Along with invasive and non-invasive analyses of lung function, the researchers quantified prostanoid levels and inflammatory cells and mediators in brochoalveolar lavage fluid to investigate differences between COX-1 transgenic and wild-type control mice. Experiments with mice that were also genetically deficient in COX-2 enabled the researchers to control for the potentially confounding effects of COX-2 up-regulation.

Beneficial effects of COX-1 overexpression were observed on airway responsiveness in naïve mice, but allergic airway inflammation and associated functional alterations were not improved. The researchers proposed that other genetic and pharmacologic strategies designed to alter the airway level of specific prostanoids or to target downstream signaling events may be even more beneficial in improving basal lung function and might prove clinically useful in alleviating allergic airway inflammation and hyper-responsiveness.

Citation: Card JW, Carey MA, Bradbury JA, Graves JP, Lih FB, Moorman MP, Morgan DL, DeGraff LM, Zhao Y, Foley JF, Zeldin DC. 2006. Cyclooxygenase-1 overexpression decreases basal airway responsiveness but not allergic inflammation. J Immunol 177(7):4785-4793.

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Combined Method for Studying Key Enzyme in DNA Replication and Repair

NIEHS-funded researchers from the Laboratory of Structural Biology, in collaboration with UNC chemists, have demonstrated the insights to be gained from combining protein crystal structures of DNA polymerase beta with high level Quantum Mechanics/Molecular Mechanics (QM/MM) calculations to better understand the chemistry at the atomic level for correct insertion by DNA polymerase beta (pol beta). The use of QM/MM calculations allows for quantum level calculations at the active site while still taking into account the entire protein/DNA environment. The crystal structure used for the study contained a non-hydrolyzable incoming nucleotide triphosphate. Thus, the starting structure for theoretical analysis contained all the atoms, including the two metal ions, required for catalysis.

Since the starting geometries are very near those of the transition state, it becomes possible to mimic the actual incorporation event. The marriage of the crystallography and theory thus provides unusual insight into the chemistry behind DNA replication.

Citation: Lin P, Pedersen LC, Batra VK, Beard WA, Wilson SH, Pedersen LG. 2006. Energy analysis of chemistry for correct insertion by DNA polymerase beta. Proc Natl Acad Sci U S A 103(36):13294-13299.

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Engineering RNA-Binding Proteins

Two DIR researchers in the NIEHS Laboratory of Structural Biology have demonstrated the potential for using a Puf family protein, Pumilio1, as a scaffold for engineering RNA-binding proteins with a designed sequence specificity. Puf family proteins regulate germ-line stem cell development, a role they perform both in lower organisms and likely in humans.

Researchers created mutations of *Homo sapiens* Pumilio 1 homology domain (hsPUM1-HD) to alter sequence specificity and performed RNA-binding experiments to determine binding specificity for cognate RNA compared to wild-type RNA. In many, but not all cases, the team was successful in designing mutant proteins with binding affinity as great or greater than wild-type proteins.

The ability to engineer hsPUM1-HD RNA sequence specificity may help scientists to probe processes that are critical for producing correct protein products in the right amounts at the right times and places. The ability to recognize specific nucleotide sequences could ultimately result in development of interventions with potential for controlling and/or correcting splicing defects that can lead to cancer and other disease and inhibiting overproduction of tumor necrosis factor alpha, which can trigger a range of inflammatory disorders.

Citation: Cheong CG, Hall TM. 2006. Engineering RNA sequence specificity of Pumilio repeats. Proc Natl Acad Sci U S A 103(37):13635-13639.

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Did You Know?

NIEHS Bids Sassaman Farewell

By Eddy Ball

The many friends and admirers of Anne Sassaman, Ph.D., at NIEHS and NIH celebrated her November 3 retirement with encomium, presents and fond reminiscences. Colleagues remembered the DERT director of twenty years for her ability to bring out the best in the people who worked with her and her uncanny knack for anticipating problems that could impede progress for division initiatives.

The institute honored her last month with a formal ceremony in Rodbell on November 1, followed by refreshments and fellowship in the lobby. Her staff held a less formal event several days earlier at DERT offices on East Campus.

NIEHS Director David A. Schwartz, M.D., moderated a series of tributes from Sassaman's staff and associates marking her retirement. (Photo courtesy of Steve McCaw)

In tribute to his supervisor's measured approach to implementing new initiatives, Bill Suk, Ph.D., jokingly credited Sassaman with "keeping me out of trouble, maybe even out of jail." (Photo courtesy of Steve McCaw)

At the more informal send-off held at East Campus, Gwen Collman, Ph.D., (left) and Dennis Lang, Ph.D., enjoyed the festivities. Rose Ann McGee and Janice Allen, Ph.D. (standing) watched from the second row. (Photo courtesy of Steve McCaw)

Pat Mastin, Ph.D., Ben Van Houten, Ph.D., and Rose Ann McGee laughed as colleagues told their favorite stories about their retiring director. (Photo courtesy of Steve McCaw)

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NIEHS Athletes Winners in Annual CFC Biathlon

By Eddy Ball

October 25 was sunny and brisk, the coldest day so far in 2006. However, the low temperatures didn't hamper the enthusiasm of the fifty-plus EPA and NIEHS employees gathered on the EPA patio overlooking the lake prior to the start of the Combined Federal Campaign (CFC) 2006 5K Biathlon and Fun Walk. The runners, walkers and cyclists queued up to sign in and warm up to the sounds of 70's Rock and Roll blaring from boom box speakers.

Moving to the beat of "Cat Scratch Fever" and "Carry on My Wayward Son," a mixed group of participants stretched their muscles and got into the spirit of the morning. They were a mixed group of fit and shapely young people, middle-aged exercise new comers and folks in their silver years who looked as though they have been exercising in one way or another all their lives.

As different as participants were from one another, they all had one goal in common. They wanted to have a good time outdoors and do some good for people less fortunate than themselves. They were raising money and awareness, in service of the annual CFC.

As they ran, walked and cycled, they were followed and protected by security personnel from EPA and NIEHS. As EPA Security Officer Andrew Almodavar described his routine for the event, "I'll count them just to make sure the same number come off the route as started it. We want folks to have a good time and come back to work safe."

Everything worked as planned. When the finish flags were down, three NIEHS employees were among the seven top winners.

Event	# Finishers	Winner
Biathlon (i)	13	1st - Wayne Dehaven, NIEHS
		2nd - BJ Collins, EPA-OARM
		3rd - Jeremy Smyth, NIEHS
		1st Woman - Leigh Herrington, EPA-OAQPS
Biathlon (t)	4	David Mintz/Hugh Crews, EPA-OAQPS
5K Run	5	Matt Martin, EPA-NCCT
Fun Walk	28	Marion Johnson-Thompson, NIEHS*
Totals	50	

*** Randomly Selected Fun Walk Finisher**

(Chart courtesy of Ellen Tvrdy, EPA-RTP 2006 CFC Coordinator)

After signing in for the event, participants took advantage of down time to stretch and warm up for the competition. (Photo courtesy of Steve McCaw)

Runners gathered at the starting line for the biathlon. (Photo courtesy of Steve McCaw)

Organizers selected Marion Johnson-Thompson as top finisher of the Fun Walk. (Photo courtesy of Steve McCaw)

Biathlon winners Jeremy Smyth (left, third place) and Wade Dehaven (first place). (Photo courtesy of Steve McCaw)

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Sharon Finds the Environment... in India

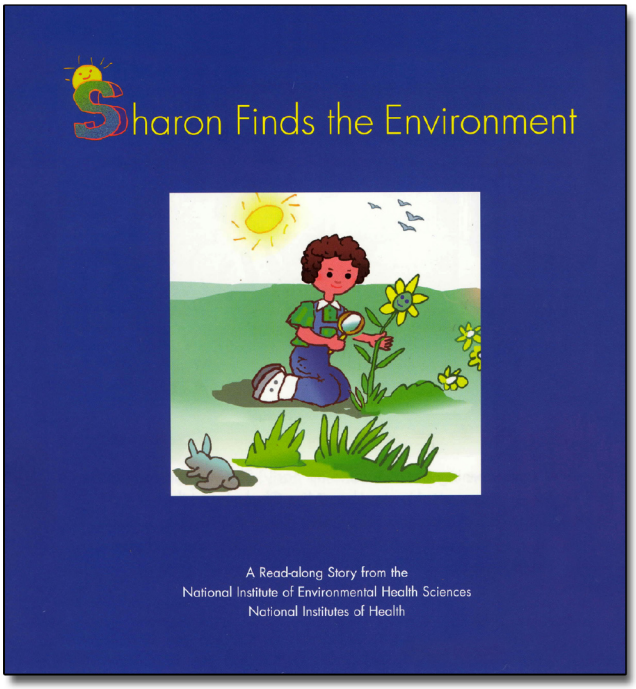
By Eddy Ball

The popular NIEHS read-along story *Sharon Finds the Environment* will soon be charming readers in India. The story was published in hard cover in 2001 and won that year's NIH Plain Language Award for author Tom Hawkins. Unlike some of the brochures, booklets, pamphlets, forms and newsletters recognized that year, *Sharon* has lived on. Now India's Allied Publishing will offer Hawkin's story of a young girl's journey to understand what "environment" means to a new generation of readers half way around the world.

Sharon has been a popular title from the beginning. Educators throughout the world have used the book in elementary school curricula, and the main character has received fan mail from readers worldwide. One especially enthusiastic fan in Cameroon wrote to ask Sharon about her age and marital status.

Because U. S. government publications are not covered by copyright, there is no way to be sure how many times *Sharon* has been published by others. The book was issued at least once in England, and it was used as the basis for a puppet show script in Canada. A google search for *Sharon Finds the Environment* produced 73 hits, many of them at university Education Department curriculum development sites and several in foreign countries.

According to Allied's Publishing Manager Tripti Sachdev, *Sharon* offers Indians "child-friendly stories" to help children "meet the challenges posed for the protection of the environment." Sachev plans to publish an affordable edition of the story with new illustrations that will appeal to children in India. The first printing, due out in December, will be in English, but the publisher is also considering translating the text into Hindi.



With the help of this popular NIEHS publication, millions of readers in India soon will have a chance to "find the environment" for themselves.

Allied Publishers was founded in 1934 and acquired by the Sachdev family in 1947, the year that India achieved independence from Great Britain. Allied has headquarters in New Delhi, with nine offices in major Indian cities. It is a wholly Indian enterprise, which produces educational texts for all age groups in addition to technical, scholarly and popular titles, and imports books from a long list of foreign publishers.

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Upcoming Distinguished Lecture

By Eddy Ball

Aaron J. W. Hsueh, Ph.D., will present the next talk in the 2006-2007 NIEHS Distinguished Lectures series at 11:00 AM December 12 in Rodbell Conference Center. Hsueh is a professor and Division head in the Division of Reproductive Biology, Department of Obstetrics and Gynecology, Stanford University. His topic will be "Coevolution and Bioinformatic Discovery of Polypeptide Ligands and Receptors."

Hseuh has contributed to the field of ovarian research by investigating follicular cell apoptosis, the molecular biology of gonadtropin receptors, and the gonadtropin and growth factor actions in the ovary. Hsueh's interests in reproductive biology include hormonal genomics, and his group has discovered several polypeptide hormones and receptors.

Laboratory of Signal Transduction Supervisory Biologist John Cidlowski is the sponsor for Hsueh's lecture.

Distinguished Lecturer Aaron Hsueh (Photo courtesy of Aaron Hsueh)

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Also Upcoming

December 1 in Rodbell beginning at 7:30 AM — NTP Board of Scientific Counselors

December 4 – 6 off-site at the Friday Center — Empowering Environmental Health Sciences Research with New Technologies: A Conference on Omics Applications in the Environmental Health Sciences

December 7 Rall Mall beginning at 7:30 AM — Holiday Craft Fair

December 12 in Rodbell at 11:00 AM — Distinguished Lecture by Aaron Hsueh

December 14 in Rodbell 1:00 – 3:00 PM — NIEHS Awards Program and Holiday Reception

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