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NIEHS Spotlight

Science Notebook

NIEHS Spotlight

Council Backs Transparency and Stakeholder Involvement

By Eddy Ball

The NIEHS National Advisory Environmental Health Sciences Council conducted its 122nd regular meeting in Rodbell Auditorium on September 17 and 18. Chaired by Acting Director Sam Wilson, M.D., the group's deliberations and comments throughout the proceedings returned to the importance of transparency and stakeholder involvement in NIEHS operations.

In his Director's Report, Wilson outlined his priorities as acting director and addressed recent leadership changes at the Institute. Council members expressed support for Wilson's commitment to transparency in the management of the Institute and to outreach efforts to engage stakeholders. Council members also asked to receive more in-depth information in the future to help them serve more effectively as "ambassadors" for environmental health science and for NIEHS.

To the gratification of several members, including Lisa Greenhill of the Association of American Veterinary Medical Colleges, Wilson forecast an invigoration of community-based research initiatives as a part of boosting stakeholder involvement. Part of the process of re-visiting the Strategic Plan, he explained, will be an assessment of the relative priority of its objectives in the larger NIEHS/NIH mission of promoting public health.

Early in the meeting, members heard briefly from William Martin, associate director of Translational Biomedical Research, about the search for a new editor-in-chief of *Environmental Health Perspectives* (see related story). Martin, who is the selecting official for the position, outlined the "open and inclusive" process of choosing the new editor — a process that Human Resources staff have described as "unprecedented" in its efforts to engage interest groups within the Institute in the decision-making process.

Wilson presided over the Council meeting. He addressed leadership changes at the Institute and championed a spirit of openness and inclusiveness. (Photo courtesy of Steve McCaw)

Bill Suk, Ph.D., in his new role as acting deputy director (Photo courtesy of Steve McCaw)

Council members Joe Graziano, Ph.D., and Stephani Hines asked for more detailed minutes as record of the council meetings. (Photo courtesy of Steve McCaw)

Later that afternoon, Martin reported on the EHP Roundtable. Held on July 27, the roundtable meeting was a listening session that included 16 stakeholders, among them council members Stephani Hines and Ken Ramos, Ph.D. Attendees addressed budget and editorial concerns in an exchange that Martin characterized as "the start, not the end of building trust."

Assistant to the Acting Director Sally Tinkle, Ph.D., proposed a protocol for gathering stakeholder input through a series of independent "stakeholder consultations" that would be publicized and open to the public. Her emphasis on the report aspect of the process prompted suggestions from council members for translating information gathered at these consultations into specific actions that can boost stakeholder participation in policy and decision making.

On September 18, NTP Associate Director John Bucher, Ph.D., presented a report on developments within his group. In addition to enumerating the progress in work on alternatives to animal testing and reports on Bisphenol A, Bucher discussed NTP-initiated audits of contracts and measures to strengthen internal safeguards against potential conflicts of interest.

As the public session came to a close on September 18, four of the five outgoing members gave brief parting presentations — all framed by their unqualified support of the NIEHS mission and its distinctive character as the only "environmental" institute within NIH (see related story).

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Jennifer Sass of the Natural Resources Defense Council attended the meeting as a representative of the NIEHS Public Partners, a stakeholder outreach initiative by the NIEHS Office of Science Policy. (Photo courtesy of Steve McCaw)

In order to ensure that every meeting has an accurate and complete manuscript as historical record, NIEHS included a court reporter for the first time at the September meeting. (Photo courtesy of Steve McCaw)

Tinkle's proposal was designed to affirm the commitment of NIEHS to the mission of protecting public health. She described the Stakeholder Consultation Program as a way of engaging stakeholders and getting their input to Council and NIEHS management. (Photo courtesy of Steve McCaw)

The Report of the Associate Director of NTP recounted the NTP efforts to address potential conflicts of interest for contractors. (Photo courtesy of Steve McCaw)

Retiring Council Members Bid Colleagues Farewell

By Eddy Ball

The NIEHS National Advisory Environmental Health Sciences Council, along with community stakeholders and NIEHS staff, were presented with humorous and at times moving messages from four of its members, whose four-year terms expired with the September 17-18 meeting. Their parting remarks, while not devoid of constructive advice, underscored the depth of their collective commitment to the Institute and its science.

The retiring group included Teresa (Teri) Bowers, Ph.D., of the Gradient Corporation, private practice attorney David Lohsee, J.D., Martin Philbert, Ph.D., of the University of Michigan, and Peter Spencer, Ph.D., of Oregon Health and Science University. Also retiring is University of Washington scientist Elaine Faustman, Ph.D., who was unable to attend the meeting.

Referring to the candor of her parting comments, Bowers, center, joked, "The worst anyone can do to me now is make me serve on another council". (Photo courtesy of Steve McCaw)

Proceeding in alphabetical order, the meeting heard first from Terri Bowers, who reflected on the group's determination when they were appointed in 2003. "The five of us who came on at that time had the same attitude that we were not going to be a rubber stamp council," she said "[and] I'm very pleased that everybody who has come on after us also has that attitude."

Philbert's remarks, at times critical, humorous and optimistic, were offered in the context of sincere gratitude for his long relationship with NIEHS. "My career is owed to this institute," he said at the beginning of his talk. (Photo courtesy of Steve McCaw)

Noting that "what was appropriate at this point was to open the window and let the fresh air and sunshine in," David Lohsee pointed to advantages for the Institute now that the public is paying so much attention to NIEHS. "We can be your ambassadors," he maintained, "We want to broadcast the good work that's done here, [and] you have to give us that opportunity.… More than any other institute, your potential to produce what I think are really dramatic and useful results to benefit people of all nations is almost limitless."

Like Lohsee, Martin Philbert focused on the opportunities of what he described as "difficult" circumstances. "There are people around this country who know not of the Institute of Environmental Health Sciences or its mission or the work that's done here who are now looking at you," he argued. "It's an opportunity here to sell the mission, to sell the work that you do and its importance to the American people. Use that time wisely."

Not surprising to anyone who has watched him at Council meetings, Peter Spencer took an entirely different approach to saying farewell to his colleagues by creating an imaginary scenario. “Rather than give my own comments, let me conjecture the comments of an extraterrestrial investigator charged with figuring out how *homo sapiens* is doing in learning about the causes of diseases and reporting back to central command somewhere in outer space.”

Despite Earth’s enormous problems with the environment and humankind’s ignorance and reluctance to face them, Spencer’s story said, “There’s a spot located somewhere in North Carolina where things are coming together in a remarkable way. In their new programs in global environmental health, they are clearly understanding that *homo sapiens* is a single species with common environmental threats which can pass over territorial boundaries, and that they’re all in the same boat together.”

“This is very encouraging,” Spencer said as he ended the story. “The place to invest and the place to keep your eye on in the future is that little spot in North Carolina.”

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Division of Extramural Research and Training Acting Director Dennis Lang, Ph.D., left, smiled along with Wilson, center, and Budget Officer Lori Johnson as they listened to the outgoing members. “I think you’ve set a bar on closing comments by retiring members,” Wilson remarked. “I can only wish my colleagues here good luck trying to reach it.” (Photo courtesy of Steve McCaw)

Lohsee reminded his colleagues, “As I leave this council be assured that I will be in the front row supporting you, and I’ll be uncompromising in my expectations.” (Photo courtesy of Steve McCaw)

Spencer’s fable may have been fanciful, but his profound commitment to the future of environmental health science struck a chord with everyone who listened. (Photo courtesy of Steve McCaw)

Unfortunately, Elaine Faustman, shown here at the May Council meeting, was absent for her final meeting. (Photo courtesy of Steve McCaw)

NIEHS Leads Trans-NIH Initiatives

By Eddy Ball

During its September 17-18 meeting, the NIEHS National Advisory Environmental Health Sciences Council heard updates on NIEHS involvement in two major trans-NIH initiatives investigating the interplay of genetic and environmental factors in the development of human diseases.

Council first heard a presentation on the Genes, Environment and Health Initiative (GEI) by Gwen Collman, Ph.D. chief of the Susceptibility and Population Health Branch in the Division of Extramural Research and Training (DERT). Shortly afterwards, Acting Director Sam Wilson, M.D., stood in for Office of Director (OD) Special Assistant Brenda Weiss, Ph.D., who is the working group leader, and presented a status report on the Roadmap (RM) 1.5 Epigenomics Initiative.

According to Collman, the GEI aims to accelerate understanding of genetic and environmental contributions to health and disease through a two-pronged approach combining genotyping and the development of next-generation exposure-measurement technologies. The genome-wide association study component will be led by the National Human Genome Research Institute (NHGRI). The Exposure Biology Program, which makes up the other component of GEI, is being coordinated primarily by the NIEHS in partnership with three other institutes and centers (ICs).

Collman expects the expanded data collection that will emerge from the GEI exposure biology component to increase several fold the power of large epidemiological studies. Miniature, light-weight environmental sensors will provide a level of accurate, real-time data on exposures that surveys alone are incapable of supplying. (Photo courtesy of Steve McCaw)

Trans-NIH Team Work

NIEHS staff in these initiatives represent DERT, OD, Office of Management (OM) and the National Toxicology Program (NTP). They are working with their colleagues from NIEHS and other ICs to maximize resources from across NIH in a concerted effort to address human disease.

David Balshaw, Ph.D., DERT

Linda Bass, Ph.D., DERT

John Bucher, Ph.D., NTP

Gwen Collman, Ph.D., DERT

Christie Drew, Ph.D., DERT

Lerlita Garcia, DERT

Jerry Heindel, Ph.D., DERT

Laurie Johnson, OM

Pat Mastin, Ph.D., DERT

Kimberly McAllister, Ph.D., DERT

RoseAnne McGee, DERT

Srikanth Nadadur, Ph.D., DERT

Terry Nesbitt, Ph.D., DERT

David Schwartz, M.D., OD

Dan Shaughnessy, Ph.D., DERT

Anne Thompson, OD

Sally Tinkle, Ph.D., OD

Fred Tyson, Ph.D., DERT

Molly Vallant, Ph.D., NTP

Brenda Weis, Ph.D., OD

Sam Wilson, M.D., OD

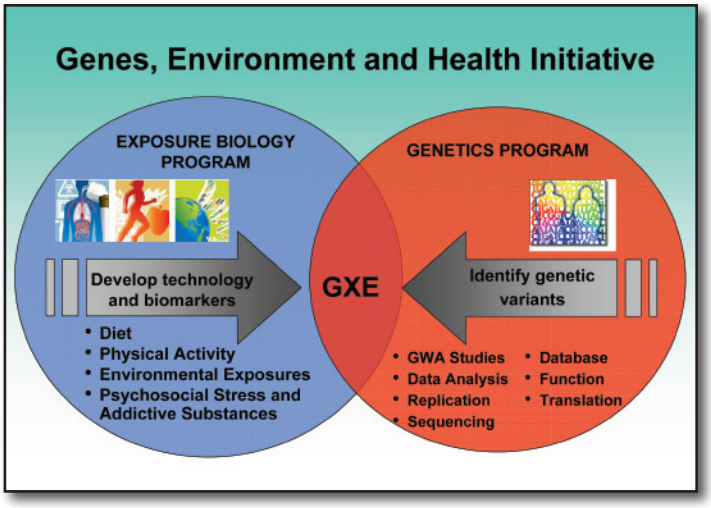
Leroy Worth, Ph.D., DERT

The genetic component of GEI uses a strategy which relies on the newfound ability to swiftly identify genetic differences throughout the genome between people with an illness and those who are healthy. This research will lead to an understanding of the underlying genetic contribution to the disease through studies of 15 complex diseases or pathological traits.

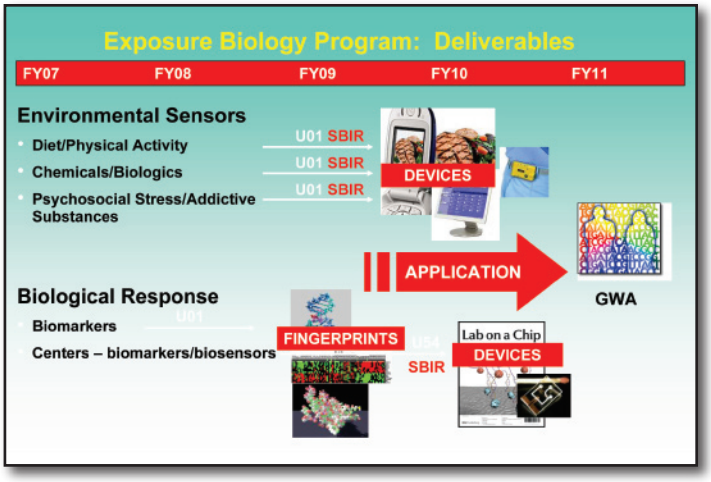
The exposure component of the initiative will support interdisciplinary teams of basic scientists, bioengineers, physician-scientists and others working toward three goals:

- Developing environmental sensors for measuring exposures to toxins, dietary intake, physical activity, psychosocial stress and addictive substances
- Identifying biomarkers in the human body that indicate activation of disease mechanisms such as oxidative stress, inflammation and DNA damage
- Integrating sensor and biomarker technologies

GEI research will span four fiscal years, FY2007-FY2010, with projected funding of $98.6 million for the genetic component and $88M for the exposure biology component. A distinctive feature of the grants under this initiative is a provision allowing Intramural researchers to compete for funding.



This graphic illustrates the area of interaction of genetic and environmental factors involved in the development of disease. (Graphic courtesy of Gwen Collman)



The sensor data and biomarkers that the Exposure Biology component develops will help researchers identify which genetic factors make people more susceptible to disease. (Graphic courtesy of Gwen Collman)

Wilson is serving as a co-chair of the Epigenomics Initiative along with Nora D. Volkow, M.D., director, National Institute on Drug Abuse (NIDA), and James Battey, M.D., director, National Institute on Deafness and Other Communication Disorders. The initiative is investigating the role of environmental exposures in triggering the epigenetic changes responsible for silencing or over-expressing genes implicated in a host of diseases. The program's working group includes 59 scientists representing 16 institutes and the NIH Office of the Director — including 12 NIEHS researchers.

Wilson outlined the four objectives of the Epigenomics Initiative:

- To establish an international committee on standard practices and platforms, develop new antibody reagents and create a reference epigenome database
- To develop epigenomic mapping data and infrastructure to facilitate research in human health and disease
- To evaluate epigenetic mechanisms in aging, development, environmental exposure (physical, chemical, behavioral, social environments) and modifiers of stress
- To develop new technology for single cell analysis and remote imaging of epigenetic activity in cells, tissue and whole animals

The initiative will orchestrate research activities under five types of Requests for Applications (RFAs). NIEHS is coordinating RFA1, totaling $50M to fund Reference Epigenome Mapping Centers, and RFA2, to support projects on epigenetic alterations related to aging, development, environmental exposure and modifiers of stress through an $88M allocation of RM/IC funds. NIDA will coordinate RFA3, funding data and computational infrastructure for Mapping Centers ($12M), and RFA 4, to develop new technology/tools for epigenetics ($42M).

Coordinated by the National Institute on Diabetes and Diseases of the Kidney, RFA5 involves $15M to fund the discovery of novel, stable epigenetic marks in mammalian cells. The National Center for Biotechnology Information (NCBI) will spend $12M to develop a publicly accessible epigenomic database.

The Epigenomics Initiative funding is expected to total over $219 M spread over FY2008 to FY2015, along with a $3 M "jump start" allotment for FY2007 planning and coordination.

The initiatives constitute some of the most fundamentally transformative research currently underway at NIH. The design of the initiatives offers both of them the potential for achieving translational results with significant clinical applications.

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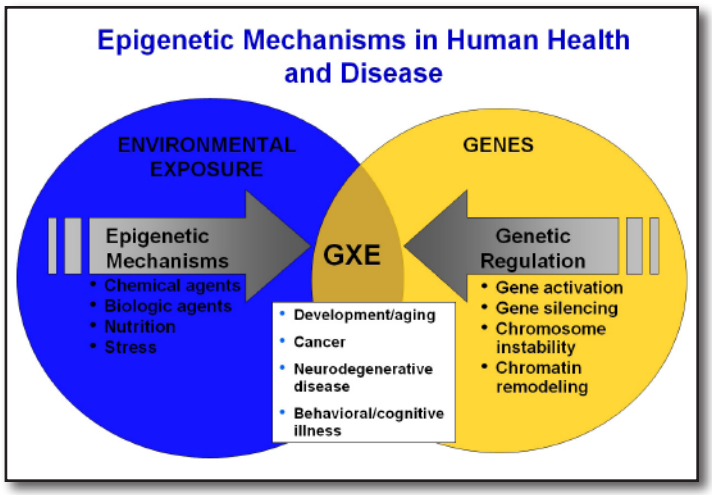
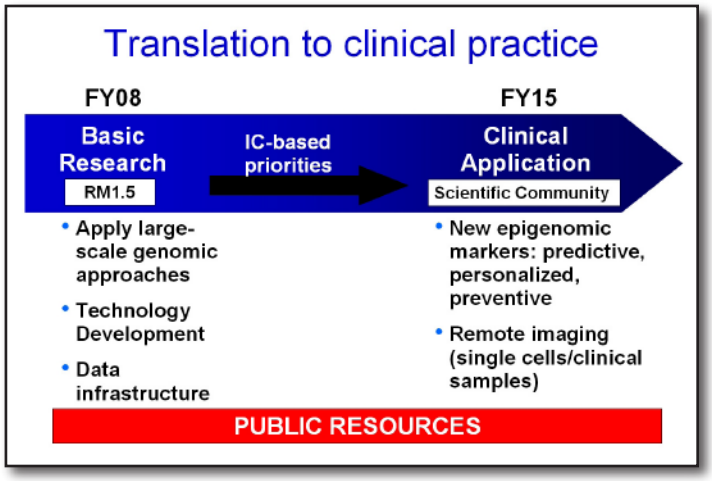


The schematic in Wilson's presentation was similar, but the focus of the Epigenomics Initiative is on the potentially reversible changes in gene expression patterns triggered by environmental exposures. (Graphic courtesy of Sam Wilson)



The translational potential of the Epigenomics Initiative is significant. Both projects promise to lead to development of new strategies for the prevention and treatment of a broad spectrum of conditions, ranging from addiction and inflammation to birth defects, chronic diseases and cancers. (Graphic courtesy of Sam Wilson)

Conference Looks to Future of Research on Endocrine Disruption

By Eddy Ball

NIEHS and the U. S. Environmental Protection Agency (EPA) sponsored a meeting in Durham on August 27-29 for scientists with regulatory, public health and research interests in the area of endocrine disrupting compounds (EDCs). Held at the Durham Marriott at the Civic Center and attracting nearly 250 participants, the meeting focused on the topic "Future Research on Endocrine Disruption: Translation of Basic and Animal Research to Understand Human Disease." The conference was organized by staff in the NIEHS Division of Extramural Research and Training Cellular, Organ and Systems Pathobiology Branch (COSPB) and their colleagues.

The Durham Civic Center offered meeting organizers the space and resources needed to accommodate 250 attendees, eight break-out discussion groups and a 72-display poster session. The facility promoted informal exchanges among attendees during breaks and meals. (Photo courtesy of Steve McCaw)

The impact of EDCs on human health remains a controversial topic among the research and regulatory communities. According to conference organizers, more than two decades of research has shown clear and adverse health effects in animal tests, but it has been difficult to develop a consensus among scientists regarding the effects in humans — a concern that inspired the meeting's innovative agenda to expand the scope and raise the visibility of research in this area.

The meeting included morning lectures, afternoon disease-focused breakout group sessions and a poster session. In addition, a special early-bird session addressed specific student needs, such as career choice and special grant programs for trainees and junior investigators.

The meeting opened with meeting chair COSPB Health Scientist Administrator Jerry Heindel, Ph.D., expressing his pleasure with the large turnout. "When we set up this meeting, we were hoping to get 150 people," he said. "We actually had to shut off registration early. For us, that's really exciting because it says that the research community is as interested in endocrine disruption research as we are at NIEHS."

Heindel expressed his hopes that the meeting would serve "to stimulate interest in the field overall, to stimulate focus on disease endpoints and the science needed to prove [or disprove] the endocrine disruptor hypothesis, and to stimulate interactions and collaborations that are going to help move the field forward." (Photo courtesy of Steve McCaw)

The conference was divided into four sessions:

- Translation of Animal and Human Data, with talks on DES (Diethylstilbestrol), Testicular Dysgenesis Syndrome, Dioxin and Endometriosis, PCBs (Polychlorinated biphenyls), Thyroid Function and Behavior, and Arsenic and Diabetes.
- Mixture Studies and Biomarker Development in Human and Animal Studies, with discussions of Concepts, Experimental Approaches and Implications for Risk Assessment, Biomonitoring Data, Genomic and Proteomic Biomarkers of Bisphenol A in the Mammary Gland, and Phthalate Exposure and Male Reproductive Tract Abnormalities.
- Role of Genetics and Epigenetics in Response to EDCs in Animal and Human Studies, with talks focusing on Genetic/Molecular Epidemiology and Epigenetics for the Toxicologist and Epidemiologist (see article in Science Notebook)
- Designing Animal Studies for Maximal Impact on Policy, with discussions of EDC Research and Risk Assessment from an EPA perspective and an overview of EDC Research Lessons Learned.

William Martin, M.D., associate director for Translational Biomedical Research at NIEHS, encouraged attendees to look into funding opportunities under the year-old trans-NIH Clinical and Translation Science Awards (CTSA) Program. "There's no question, I think, that endocrine disruptors would fit that [program's] mandate." (Photo courtesy of Steve McCaw)

NIEHS Supervisory Biologist Retha Newbold gave a keynote address on "DES Translation and Lessons Learned." Research into this "poster child" of endocrine disruption helped scientists develop a model for looking at other EDCs of concern, such as Bisphenol A, tamoxifen and genistein. (Photo courtesy of Steve McCaw)

The meeting concluded with disease-focused reports by groups assessing the strength of evidence linking EDCs to specific conditions:

- Thyroid Dysfunction
- Testicular Dysgenesis
- Obesity/Diabetes (Developmental Basis of Obesity)
- Male Reproduction (Fertility/Prostate Cancer)
- Puberty/Polycystic Ovary Syndrome/ Endometriosis/Fibroids/Premature Menopause
- Female Reproduction (Fertility)
- Breast Cancer
- Neurobehavior/Neurodegeneration

The groups assessed future research directions and resource needs as they endeavored to answer the conference challenge: "What should be done to develop the specific data (and what are those data) that would provide… 'strong compelling data' of EDC effects on a specific disease/dysfunction in humans?" (see text box)

Heindel plans to publish specific recommendations by the groups. The groups called for expanding testing using "omics" platforms to uncover distinctive signatures of EDCs and their effects, as well as to discover more

sensitive biomarkers. “Omics” applications, such as proteomics and genomics, are distinguished by their unbiased and global analyses performed using high-throughput technology.

Discussants saw access to human tissue as an important step toward understanding the parallels between animal and human exposures and making the translation from animal results to health effects in humans. Because of the ethical concerns about conducting research on pregnant woman and fetuses, it will be critical, the groups agreed, to identify markers in such surrogate tissue as urine through validating biomarkers in available human reproductive media, such as amniotic fluid.

The groups also expressed a need to understand more completely the effects of cumulative exposure and the timing of exposure windows, deficits that have made it harder to demonstrate the effects of EDC exposure in humans. Work is needed as well in understanding the effects of mixtures on exposures and in developing dose response patterns.

EPA Toxicologist Susan Makris, Ph.D., outlined the differences between peer-reviewed studies and the highly structured guideline studies valorized by regulators and policy makers. Makris encouraged attendees to design and conduct their studies to provide information that will be applicable within the risk-assessment paradigm. (Photo courtesy of Steve McCaw)

University of London Pharmacologist Andreas Kortenkamp, Ph.D., tackled the topic of mixtures. He presented what he billed as a “how-to” talk on mixture analysis in epidemiological studies. (Photo courtesy of Steve McCaw)

Several scientists from NIEHS with interests in EDCs and translational medicine were on hand for the meeting. Epidemiologist Walter Rogan, M.D., shown in foreground, has faced similar translational issues with research in the Soy Estrogens and Development (SEAD) project. (Photo courtesy of Steve McCaw)

EPA Toxicologist Linda Birnbaum, Ph.D., closed out the lecture portion of the meeting with an inspiring call to move forward with EDC research. Her talk reflected the divided opinions of researchers and regulators in regard to EDC health effects. (Photo courtesy of Steve McCaw)

"Setting the Stage" — Opening Remarks from Jerry Heindel

As the first session of the conference began, Heindel presented the audience with the hypothesis behind NIEHS funding of EDC research. "This is the hypothesis we're working under: that hormonally active compounds in the environment, called endocrine disruptors, are having a significant impact on human health, and that impact is the increase of disease and dysfunction," he said. "In order to protect and improve health… we have to focus more on integration and translation of research."

The missing ingredient, Heindel continued, is human data. Even after more than 20 years of research, the data have not been forthcoming, and without that body of evidence, convincing skeptics of the health threats of EDC exposure will continue to be difficult. Heindel pointed to major challenges for researchers:

- The changes resulting from EDC exposure are small and functional — and more sensitive endpoints than are usual or, in many cases, possible in human studies are needed
- The role of polymorphisms compounds the problems of research — highlighting the need for a comprehensive genomic approach
- Environmentally relevant exposures appear to be low — mandating the development of very sensitive personal exposure assessments
- The dose responses are likely "non-monotonic" in many cases — pointing to the need for calculating extended dose responses
- The effects are expected to be due to multiple chemicals with varying sensitivities and half-lives — indicating the need for a sophisticated mixtures approach
- The effects are probably due to multiple exposures — underscoring the need for a life-span approach to exposure
- Exposures at various developmental stages — from conception to adulthood — appear to interact to produce adverse health effects in adulthood
- Some of the effects may be trans-generational, requiring researchers to look beyond the initial exposures to understand the full range of effects
- Current assessment approaches are inadequate — researchers must be willing to take advantage of new technologies to improve exposure assessment and biomarkers of exposure and toxicity

"Many of us will have to shift our focus to disease and dysfunction, instead of just toxicity," Heindel argued. Effective translational research will depend on integration of all aspects of research. Heindel pointed to work needed in the areas of technology development and bioinformatics, understanding mechanisms, clinical assessment, and applications and interventions.

While epidemiology is challenging, Heindel observed, "A good epidemiological study can be worth a hundred animal studies. And there are nice examples of that with DES and [1,2]-dibromo-[3]-chloropropane, where one good human study was enough to get rid of that chemical."

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Obesity and Built Environment Progress Reports

By Eddy Ball

The Division of Extramural Research and Training (DERT) hosted a meeting on September 5 and 6 for investigators funded through the Obesity and Built Environments program. The researchers gathered at the Sheraton Imperial Hotel in Research Triangle Park to present progress reports on their grants and share their successes and challenges with their colleagues. The series of presentations was chaired by Mike Humble, Ph.D., health scientist administrator in the DERT Cellular, Organ and Systems Pathobiology Branch.

Humble, a good-natured chair with a ready smile and wry sense of humor, nevertheless ran a tight meeting. He used numbered cards to keep speakers within their time limits, and the meeting ended 20 minutes early. (Photo courtesy of Steve McCaw)

The group included epidemiologists, public health professionals, behavioral and social scientists, architects and planners engaged in innovative interdisciplinary research into ways to impact the obesity epidemic through understanding and modifying environmental influences. The program is funded by NIEHS in conjunction with three other NIH institutes and centers and two centers within the Centers for Disease Control and Prevention.

The program, which began project funding in September 2005, supports seven four-to-five-year R01 projects to provide insights into treatment mechanisms or to develop models for prevention of obesity and related health problems. It also funds seven two-year R21 grants supporting the development and validation of built-environment measures and methods of data collection.

John MacDonald, Ph.D., reported on progress with his team's study of the "Impact of Light Rail on Physical Activity and BMI" among 800 residents living along the proposed corridor in Charlotte. (Photo courtesy of Steve McCaw)

The grantees are working in cities, suburbs, college and corporate campuses, and rural areas across America to uncover the physical and psychological factors that encourage physical activity and discourage unhealthy eating habits. These factors range from the potential impact of Charlotte's light rail system on physical activity (PA) and body mass index (BMI) of residents to the effects of housing density and distance from homes to consolidated schools in 29 rural communities in New Hampshire and Vermont on adolescent overweight.

Unlike much of the bench science supported by intra- and extramural NIEHS funding, most of the Obesity and Built Environment grantees rely on measuring instruments that investigators have had to develop themselves or adapt from other contexts. Several of the projects have needed to refine city planning and administration data bases, census figures and socioeconomic data, business directories and public works mapping to characterize

neighborhoods. In a study of PA, nutrition and environment in the neighboring border cities of El Paso, Texas and Ciudad Juarez, Mexico, investigators field tested a belt-mounted monitoring system that combined Global Positioning System data logging receivers and digital cameras with triaxial accelerometers to supplement seven-day diet diaries kept by study participants.

In a project studying childcare center preschool play areas by researchers in North Carolina State University's College of Design, a landscape architect and his team are relating engineering and aesthetic criteria, such as slope, shade, appearance and ground surface to levels of PA. The Lean and Green in Motown Project in Detroit is assessing a matrix of methods, including spatial indicators, typologies, resident perceptions, BMI and obesity-related biomarkers, for assessing the neighborhood environments and their impact on health.

Lead-off speaker Wenjun Li enjoyed a humorous comment during the second day of the meeting. During his talk, he got a few laughs from his colleagues with the coined terms "obesocape" and "obesogenic." (Photo courtesy of Steve McCaw)

Built Environment, Obesity and the Disabled in Chicago

With her background in physical therapy, Investigator Jennifer Rowland, Ph.D., fits well with the University of Illinois at Chicago (UIC) Health Empowerment Zone for People with Disabilities Project. Rowland and the project's principal investigator, James Rimmer, Ph.D., are professors in the Department of Disability and Human Development, part of the College of Applied Health Sciences at UIC. The aim of their project is to create a model program for improving access to the built environment, resulting in improved health and the reduction of secondary conditions among people with mobility disabilities.

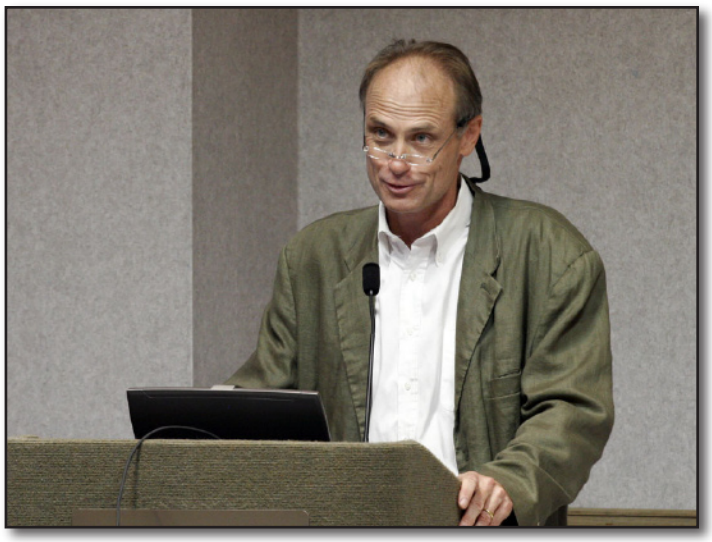
The two-phase project is developing measurement instruments and using a community-based participatory research model to implement its model. Investigators have developed a multilevel intervention involving partnerships between UIC and the Illinois Americans with Disabilities Act Project, the Chicago-based American Planning Association and the Urban Transportation Planning Center at UIC.

The research team is using pre- and post-intervention telephone surveys of 120 subjects recruited at an Access Chicago Health Fair to evaluate the project's effects on physical activity, obesity and quality of life measures. The mean age of subjects is 55 years, and mean BMI is 36.1. Fifty-five percent are unable to work, and 73 percent use multiple devices for mobility. Physical activity levels are low, and most report secondary health problems that are not directly related to their mobility deficit.

Phase one of the project, the subject of Rowland's presentation, involves creation of a three square-mile Health Empowerment Zone in downtown Chicago, creating a "natural laboratory" for observing the impact of improved access on the physical activity and eating behaviors of residents with mobility limitations. In conjunction with city government, non-profit organizations and business owners, the project is overseeing improvements to walking networks, parks and recreation facilities, mass transit, and grocery stores and retail outlets. Project staff are educating businesses about the accessibility needs of persons with disabilities and recognizing disability-friendly facilities with special stickers they can display at their entrances.

Phase two of the project will introduce a proactive effort to alter behaviors with a "Ticket to Health" Campaign. This campaign will involve the distribution of pre-paid vouchers to a random sample of phase-one participants. The participants will be able to redeem their vouchers for specific products from participating businesses in the Health Empowerment Zone. These health-promoting goods and services may include healthy foods from disability-friendly grocery stores, sessions at community fitness and recreation centers, and travel on mass transit.

In a time of flat budgets, Art Wendel, M.D., could offer little more than "continued interest at CDC in built-environment research" and its relationship with the agency's Healthy Communities goal and climate change initiative. (Photo courtesy of Steve McCaw)



Planner Peter Owens of Smart Mobility, Inc., reminded his colleagues of the rural side of Obesity and the Built Environment Research with his profile of the small towns in New Hampshire and Vermont where his team is studying the environmental and family influences on adolescent overweight. (Photo courtesy of Steve McCaw)

While the R21 projects are research-enabling efforts to develop and validate measurements, factors and outcomes, the R01 projects typically see their translational component in terms of education, behavioral modification, publications and policy making.

To that end, several projects have formed working alliances with government officials, non-profit organizations and community organizers to impact policy. The University of Massachusetts project, for example, has submitted its obesity and neighborhood characteristics data — what researcher Wenjun Li, Ph.D., has dubbed an "Obesogenic Map" of the state — to Department of Public Health policy makers. Researchers with the University of Illinois at Chicago (see text box) have worked with the Mayor's Office for People with Disabilities and the Chicago Board of Aldermen to improve sidewalk access through public works projects and developed incentives for businesses that are making an effort to improve accessibility.

Jennifer Rowland reported on a novel translational application of built-environment research as she showed slides of public works improvements to help mobility disabled people in Chicago expand their food shopping opportunities. (Photo courtesy of Steve McCaw)

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Institute Employees Meet EHP Editor-in-Chief Candidates

By Eddy Ball

NIEHS kicked off a series of open interviews of three top candidates for the position of Editor-in-Chief of the NIEHS journal *Environmental Health Perspectives* on September 5 in Rodbell Auditorium. Facilitated by Associate Director William Martin, M.D., selecting official for the position, the series was open to all Institute employees, contractors and the public.

Martin emphasized objectivity and consistency throughout the interview series. (Photo courtesy of Steve McCaw)

The candidate interviews opened with chemist Mike Cunningham, Ph.D., of NIEHS/NTP. The interviews continued on September 6 with pharmacologist Hugh Tilson, Ph.D., of the Environmental Protection Agency (EPA), and September 13 with chemist Richard Wiggins, Ph.D., also of EPA. Each interview session followed the same format, with a welcome and introduction by Martin, a ten- to fifteen- minute talk by the candidate about his qualifications and reasons for seeking the job and 40 to 50 minutes of questions from the audience.

In their opening comments or in response to questions from the audience, each of the candidates touched on several issues, including the relationship between the journal and the Institute, the editorial balance of the publication, potential conflicts of interest, the role of the editorial board, ideas for non-subsidy revenue streams, and ways to boost the journal's circulation and impact factor.

Maintaining that there should be "no or very little influence by NIEHS" on the publication, Cunningham proposed a proactive role for the editor-in-chief, inviting impressive presenters at professional meetings to submit papers to the journal. (Photo courtesy of Steve McCaw)

Cunningham is a 20-year veteran of NIEHS who is a chemist in the Chemistry Group in the Laboratory of Pharmacology and Chemistry. He has also worked in the National Toxicology Program, the NTP Toxicokinetics Faculty, the National Center for Toxicogenomics and the ToxGroup. He has experience as an associate editor of *Toxicological Science*, an editor of *Mutation Research* and a member of the Faculty of 1000.

Tilson, a former NIEHS section head, is currently a National Program Director of Human Health Research at EPA. He has served in leadership roles in the Office of Research and Development and as the assistant laboratory director for human health and the director of the neurotoxicology division. He has edited books, served as an associate editor on three journals and held seats on several editorial boards.

Wiggins has served as senior science advisor in the National Health and Environmental Effects Research Laboratory for five years. Prior to joining federal service, he served in several academic posts, most recently as chair of the Department of Anatomy at West Virginia University. A neuroscientist specializing in under-nutrition and brain development, Wiggins was co-creator of the niche journal *Metabolic Brain Diseases* and served as its editor-in-chief.

Emphasizing teamwork and consensus, Tilson described himself as having "almost too much management experience." He presented a list of four core principles as his vision statement and described the "wall" he envisions between the editor and the Institute. (Photo courtesy of Steve McCaw)

Wiggins shared his ambition to brand EHP as "the world's platform" for environmental science and spoke confidently of raising the journal's impact factor. He promised to be aggressive in defending editorial independence. (Photo courtesy of Steve McCaw)

Brogan and Partners contract employee Joseph Tart, EHP publications director, attended the first two interviews. He was especially interested in how broadly the journal should define its subject areas. (Photo courtesy of Steve McCaw)

In order to ensure a comprehensive and open process for this important position, NIEHS convened a panel of subject matter experts (SME) to review applications received by NIH Human Resources in response the vacancy announcement. The panel included Senior Research Biologist Ken Korach, Ph.D., Laboratory of Respiratory Biology Chief Steve Kleeberger, Ph.D., Medical Corps Officer Matt Longnecker, M.D., ScD., and Office of Director Special Assistant Brenda Weis, Ph.D. The SME panel selected the top four candidates, whose applications Martin reviewed before choosing three to participate in the next phase of interviews.

An interview committee, which included the SME panel as well as EHP Writer/Editor Susan Booker and Director Emeritus Ken Olden, Ph.D., then developed a strategy for in-depth interviews of the candidates in a series of meetings with interested communities within the Institute. These interest groups included the *EHP* staff, NIEHS public community, the Division of Intramural Research, the Division of Extramural Research and Training, and the National Toxicology Program staff.

Rodbell B was more than adequate as a venue for the series. A core of vocal participants showed up at the meetings, including Toxicologist James Huff, Ph.D., foreground, and EHP Technical Publications Editor Dorothy Ritter. (Photo courtesy of Steve McCaw)

Participants were encouraged to submit their comments about the candidates to Martin for his consideration in choosing the candidate to fill the position. The search closed on September 28. Martin will make the final selection in the coming weeks.

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Media Training for Institute Scientists

By Eddy Ball

On August 24, Executive Communication Coaches Nan Tolbert and Tom Hoagwood from the Washington, D.C.-based company, The Communication Center, offered NIEHS employees strategies for managing the challenges of effectively communicating science. Their presentation, titled "Media Matters," took place in Rodbell Auditorium and covered the opportunities and pitfalls of media interviews.

Executive Communication Coach Tom Hoagwood gave several examples of how to prepare clear messages for a good media interview. (Photo courtesy of Steve McCaw)

The Friday session wrapped up the coaches' two-day visit to NIEHS. While at the Institute, the two provided personalized media training to small groups of scientists and executives who are often involved in media interviews. The training was coordinated and supported through the NIEHS Office of Communications and Public Liaison.

As part of their visit, Tolbert and Hoagwood conducted three 3.5-hour sessions of mock interviews with NIEHS scientists to mimic the experience and potential pressures of encounters with the media as they try to get the story out about what researchers are doing. During their presentation in Rodbell Auditorium, Tolbert and Hoagwood recapped the messages they had given the small groups about audience connection, message development, delivery skills and taking more control of the communication process.

According to Coach Nan Tolbert, planning ahead is just as essential for telephone interviews as it is for a filmed or recorded interview. (Photo courtesy of Steve McCaw)

Hoagwood opened the program with a reference to that "deer in the headlights" moment when unprepared interviewees receive questions that make them realize the interview has become something they didn't expect. Effective communicators are those people, he explained, who can work with the reporter as a "conduit" for the one or two quotes that will appear in a short article or the typical eight-second sound bites that are part of a radio or TV segment that lasts an average of one minute or less.

Noting that most reporters are grateful for anything that makes their jobs easier, Tolbert encouraged scientists to take a "rolodex" approach to preparing for interviews by creating bullets of interesting examples to back up their talking points and "put a face on the facts." She said, "A media interview is the last place for original thought."

To help maintain control over a media interview, the coaches cautioned, scientists should deliver the most important points up front and use verbal flagging to focus the interviewer with such phrases as "the most important point is" and "here are the three critical issues." According to Tolbert, flagging helps to guide reporters back to the points a scientist wants to make sure get included in the report.

In addition to focusing — and re-focusing when necessary by finding two or three ways to say the same thing— scientists can also maintain control by steering clear of what the coaches described as "media traps," such as repeating in the answer the negative language in a reporter's question. "It's your job to refocus and get them back onto what you want to talk about."

"Once we've got our message down, what do we do about delivering that message?" Tolbert asked. Referring to a UCLA communications study, she pointed to the power of voice tone and body language, which together make up 93% of what is important in keeping an audience engaged. During a television or radio interview, "be natural… be in the moment," Hoagwood added. Showing confidence is valuable, but, he cautioned, "If you're not the type who gestures, this isn't the time to start."

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The Friday afternoon audience took away sound advice for more effectively getting across what they want to say the next time they talk to the media. (Photo courtesy of Steve McCaw)

NIEHS News Director Robin Mackar spent most of two days working with the coaches, who are representatives of The Communications Center, in Washington, D.C. The firm's clients include major government agencies, universities, non-profits, national media and corporations. (Photo courtesy of Steve McCaw)

Science Notebook

Cancer Researcher Discusses MRP1 and GSH-dependent Transport

By Robin Arnette

The 2007–2008 NIEHS Distinguished Lecture Series opened with a seminar by Susan Cole, Ph.D., on September 11 in Rodbell Auditorium. Cole, a Canada Research Chair and Queen's University Bracken Chair in Genetics and Molecular Medicine at Queen's University Cancer Research Institute, presented "The Complex Role of GSH in the Function of the MRP1 Drug and Organic Anion Transporter." The seminar was hosted by David Miller, Ph.D., head of the Intracelluar Regulation Group in the NIEHS Laboratory of Pharmacology and Chemistry.

Cole explained all of the complexities involved in the binding of glutathione to MRP1. (Photo courtesy of Steve McCaw)

Cole is interested in studying how drugs, toxins and metabolites get into and out of cells. The protein she cloned along with colleague Roger Deeley 15 years ago — multidrug resistance protein (MRP1) — plays a major role in conferring drug resistance in cancer patients as well as protecting normal tissues from cytotoxic drugs. MRP1 is a member of the ATP-binding cassette (ABC) transporter subfamily C and is the model for what researchers know about drug and xenobiotic efflux.

Miller hosted the seminar and introduced Cole. (Photo courtesy of Steve McCaw)

But when Cole first discovered MRP1, she had no idea how complex it was going to be. "There are 49 human ABC transporters now, but when I got started in the field there were just two known human transporters," she said. "I feel sorry for people who got into the field 10 years later because there were about 35 [transporters] then, and it made the field much more difficult because there was so much we didn't know."

One of the first things transport scientists wanted to know about MRP1 was what substrates it carried across cell membranes. Cole explained that a German research group found that MRP1 had high affinity for and could transport leukotriene C_4 (LTC_4), a pro-inflammatory glutathione (GSH)-conjugated arachidonic acid derivative. Another group knocked out MRP1 in mice and demonstrated that the mice had impaired inflammatory responses, which established that LTC_4 was a physiological substrate for MRP1. "This identification made us and others start to wonder that it wasn't just this endogenous GSH-conjugated metabolite that could be a substrate for MRP1, but probably other GSH-conjugates as well," Cole said.

Other studies established that MRP1 could transport unmodified drugs, but only in the presence of GSH, so Cole and her group designed experiments that would determine the exact mechanism of action. Because estrone sulfate labeled with tritium was the most convenient GSH-dependent substrate to work with, they used it in their initial detailed mechanistic studies of MRP1-mediated GSH-dependent transport. Cole cautioned, however, that if they had used another GSH-dependent substrate, it probably wouldn't have produced the same results. The data they have generated to date is likely to be, to some degree, substrate-specific, although significant similarities are expected with other GSH-dependent MRP1 substrates.

Cole's group also performed extensive site-directed mutagenesis studies to determine which amino acids may be important for substrate binding and transport by MRP1. Their 350 point mutations of the 1531 amino acid-long MRP1 revealed phenotypes where mutant MRP1 proteins are not expressed, show global or substrate selective loss of substrate binding and/or transport activity, exhibit altered nucleotide binding and hydrolysis properties, or manifest a combination of these phenotypes.

Although Cole and her group have a better understanding of how GSH affects the transport properties of MRP1 than they did 15 years ago, there is more to learn. By continuing to look for experimental answers to their questions, they intend to fully understand the complex mechanisms that determine the ability of MRP1 to transport an extraordinarily diverse range of molecules across the plasma membrane.

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Model of MRP1 GSH-stimulated Transport of Estrone Sulfate

Results from radioligand equilibrium binding assays and other biochemical studies led Cole's group to develop the following model for GSH-stimulated transport of estrone sulfate. GSH binds to MRP1 on the inside of the cell and causes a conformational change in the transporter that opens up a high affinity site for estrone sulfate. This action allows efficient binding.

Then, when ATP binds, additional conformational changes allow estrone sulfate to be transported over to a low affinity site on the outer side of the membrane so the substrate can be released; however, the inner GSH binding site remains in a high affinity state and consequently, GSH is not transported. It is only released from the membrane after ATP hydrolysis when the binding site returns to a low affinity state. "Although incomplete, this is our current explanation of how binding of both these substrates to MRP1 occurs and can affect each other's binding, but one is transported and the other isn't," Cole stated.

William Schrader, Ph.D., deputy scientific director of the Division of Intramural Research at NIEHS, asked for more details about MRP1. (Photo courtesy of Steve McCaw)

Pesticide Exposure in Farm Worker Families

By Robin Arnette

On September 6, the American Federation of Government Employees (AFGE) Local 2923 and the NIEHS Diversity Council co-sponsored a seminar to celebrate Labor Day. Extramural Grantee Thomas A. Arcury, Ph.D., professor and director of Research in the Department of Family and Community Medicine at Wake Forest University School of Medicine, presented "Pesticide Exposure in Latino Farm Worker Families: Current Results and Ongoing Research." This was the third annual NIEHS Labor Day seminar, and it drew a large number of attendees from within the Institute, the Environmental Protection Agency (EPA) and the National Toxicology Program (NTP).

Arcury explained his findings involving farm worker families and pesticide exposure. (Photo courtesy of Steve McCaw)

Bill Jirles, President of AFGE 2923, chose Arcury because of his past involvement in policy issues important to workers and their families. "We thought Tom was a stellar choice for a Labor Day speaker due to his research and work with farm workers as well as those who advocate on their behalf," Jirles said. "Labor Day is about equality, fairness and dignity for all workers, and farm workers demonstrate the ongoing struggle for these rights."

Arcury began his talk by describing the population at the heart of his work. In the United States farm workers are generally divided into two groups: migrant and seasonal. Migrant workers change residence, usually more than 75 miles, for agricultural employment. On the other hand, seasonal workers earn their income in agriculture in certain seasons, but do not necessarily travel to work in other locales.

According to the National Agricultural Workers Survey, published by the U.S. Department of Labor, 42 percent of farm workers are migrants and 58 percent are seasonal, but these days the typical farm worker tends not to be American. Seventy-eight percent of the farm worker population is foreign-born with the majority of them coming from Mexico. Others are from Central America and Southeast Asia.

"Because half of all farm workers are undocumented," Arcury explained, "it raises lots of problems in terms of protecting their rights as workers and protecting them in terms of exposure." Since there weren't a lot of articles that dealt specifically with pesticide exposure and farm workers, Arcury and his collaborators developed two surveys, La Familia and Casa y Campos to find out more.

La Familia was carried out in 2001 in the mountains of North Carolina with 41 farm worker families participating in the study. Arcury and his colleagues went to the workers' homes and tested the floors, children's toys and the children's hands to see where the pesticides—both agricultural and residential—were coming from and where they were ending up. They found pesticides in 39 of the 41 households. "Ninety-five percent of households had pesticides on the floor, about 71 percent of the toys had pesticides, and with hands, it went to 55 percent," Arcury said. "Through our analysis, we show the pathway is that pesticides got on floors, then on toys and then on hands."

In 2004 Arcury and colleagues recruited 60 kids from farm worker households in Benson, N.C. for the Casa y Campos study. The team interviewed the mothers, collected urine samples from the children and measured 14 pesticide-specific metabolites.

"One child had no detectable metabolites, three children had seven, but most had three or more metabolites in their system," Arcury said.

Even the front row seats at Rodbell A were filled nearly to capacity — sure sign of a popular event. (Photo courtesy of Steve McCaw)

Although these studies have increased the knowledge about pesticide exposure in farm worker families, there is still much to do. Arcury and his colleagues demonstrate their commitment to policy by creating reports for state legislators and farm worker advocates, but they are also heavily involved in health education by producing and distributing videos and print materials on pesticide safety and speaking to migrant clinicians at conferences. Most of these health education materials may be found at Wake Forest's Department of Family & Community Medicine Web site.

Arcury is currently in the second year of an NIEHS community-based participatory research grant to study pesticide exposure among adult farm workers in eastern North Carolina. It is a collaborative project involving the North Carolina Farm Workers Project, Student Action with Farmworkers, Greene County Healthcare and the Columbus County Community Health Center.

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Air-Sampling Robot on Florida Beach

By Eddy Ball

During the second weekend of September, visitors to a public beach at Siesta Key near Sarasota, Fla. were treated to something entirely new as a funny looking foot-long machine raced across the sand. What sunbathers witnessed was a first in environmental monitoring — a small roving air-sampling robot capable of detecting concentrations of airborne particles just above ground level that can cause respiratory problems.

Environmental health scientist Stuart Shalat attracted more media attention than he expected at the Florida beach, including five television interviews and a National Public Radio report. (Photo courtesy of Stuart Shalat and the Robert Wood Johnson Medical School at the University of Medicine and Dentistry of New Jersey)

Robert Wood Johnson Medical School researcher Stuart Shalat, Sc.D., had traveled south to test a sensor he created as part of work co-funded by NIEHS R01 and PO1 grants. His technology is now being used as part of ongoing studies of health effects

related to Florida Red Tide at Siesta Key, the site of a 2005 outbreak. When inhaled at high enough concentrations by beachgoers, the toxin produced by the algal blooms that create red tide in coastal waters can cause respiratory problems, especially in people with asthma.

Wielding his specialized air sampler, Shalat set out to establish baseline measurements for a focused investigation of the health effects of red tide on an especially vulnerable population, very young children six to twelve months old. He will compare the results to samples he plans to collect when there is another outbreak.

Called "PIPER," for "Pre-Toddler Inhalable Particulate Environmental Robotic" Sampler, the device can mimic a toddler's environmental exposures by collecting samples through air intakes that are adjustable from 20 to 50 centimeters (approximately 8 inches to 20 inches) above the surface.

The PIPER is less than a foot long and a foot tall. Air samples enter the device through an adjustable vent and travel through tubing into a storage chamber on the chassis. (Photo courtesy of Stuart Shalat and the Robert Wood Johnson Medical School at the University of Medicine and Dentistry of New Jersey)

The robot's size is important, according to Shalat, because levels of particulates at a toddler's level can be much greater than they are at five or six feet above a surface. Particles from soil, sand or dust that is disturbed can be "re-suspended" and enter a toddler's environment, although they may pose no threat to adults and older children.

When particulates begin to settle outside the range of an adult's environment, they can still remain a hazard for small children who crawl along a surface. Toddlers are also especially vulnerable to contaminants "entrained" or tracked into houses by beachgoers.

The PIPER roamed the beach on its own, following a pattern that Shalat had programmed previously. (Photo courtesy of Stuart Shalat and the Robert Wood Johnson Medical School at the University of Medicine and Dentistry of New Jersey)

The PIPER resembles a wheeled erector-set truck with a long adjustable neck-like crane — a kind of miniature steel giraffe on wheels. The body contains a chamber where air samples are deposited on filters for analysis later in a laboratory. The autonomous robot is self-propelled and can be programmed to follow a set pattern of movement around an area.

The prototype was built at a cost of approximately $2,000 for parts. According to Shalat's grant application, the PIPER was originally proposed for detecting indoor allergens and toxins. However, the machine has performed well on playgrounds and on the level Florida beach where it sped along on its tiny tractor-like tires.

Shalat is collaborating with NIEHS P01 grantee and veteran Florida Red Tide researcher Dan Baden, Ph.D. Shalat's RO1 grant is administered through the Division of Extramural Research and Training by Health Science Administrator Kimberly Gray, Ph.D.

Working together across disciplines, oceanographers, chemists, toxicologists, public health specialists, physicians and biomedical scientists approach the problem in a "beach to bedside" manner. In addition to NIEHS, the partnership includes the Centers for Disease Control and Prevention, the Florida Department of Health, the University of Miami, the University of North Carolina, Wilmington, Lovelace Respiratory Research Institute, New Mexico, the Robert Wood Johnson Medical School and Mote Environmental Services.

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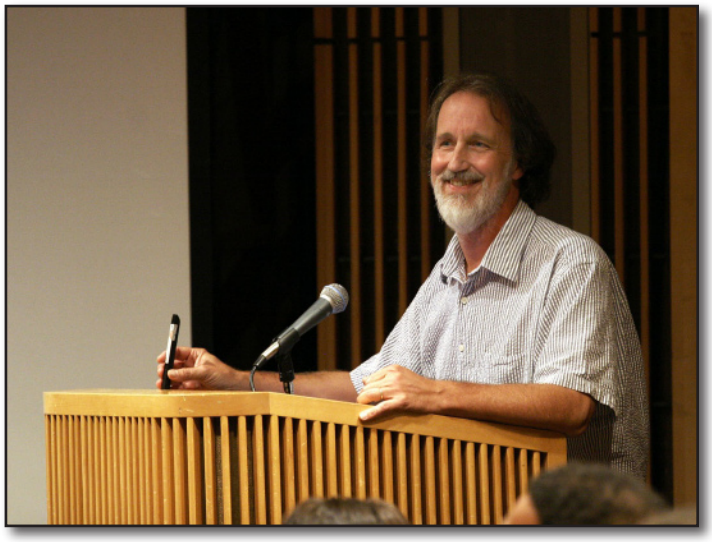
NIEHS Readies Molecular Genetics Core

By Eddy Ball

Division of Intramural Research (DIR) investigators will soon have an in-house resource for genotyping and re-sequencing, according to Senior Investigator Douglas Bell, Ph.D., spokesman for the oversight committee of the new Molecular Genetics Core (MGC). Speaking on September 20 to a group of nearly 100 scientists gathered in Rodbell Auditorium, Bell said that he expects the MGC to begin processing requests as early as November 1 — the date the online requisition site is scheduled to be fully operational.



Meeting chair Doug Bell enjoyed some of his colleagues' quips. (Photo courtesy of Steve McCaw)

The MGC Steering Committee will be responsible for approving and prioritizing requests for services along a model currently used by the Microarray Core. Bell said that most routine requests should be approved quickly, but that large and expensive special projects may require more extensive committee consideration. "We anticipate a large demand for human single nucleotide polymorphism (SNP) genotyping. But because these projects often include large numbers of samples and require many genotypes per sample, we are not sure how many of these we can take on at once."

According to Bell, the Core will eventually provide all knockout and transgenic mouse genotyping for DIR. Bell pointed to a survey indicating that 40 percent of DIR principal investigators have used genotyping of some kind and that "a significant number need it on a regular, even weekly basis.… Specifically, mouse genotyping is a huge need, there's a need for rapid turnaround, and it's proven to be very expensive when done by contract."

The MGC facility was made possible by the acquisition of high-throughput, automated equipment using robotics to perform most routine mouse genotyping runs in 48 hours. Larger, more complicated "special" projects will take longer, noted Core Director Lauranell Burch, Ph.D., but, because of sample bar coding, automation and the economies of scale, the MGC will still save the Institute considerable time and money.

While Burch expects most of her initial jobs to involve mouse tail molecular genetics, the core will also be able to process all kinds of human samples and samples from other organisms used in genotyping and re-sequencing, including *Drosophila*, *C. Elegans*, yeast and *E. coli*. The facility houses equipment capable of a broad range of services:

- Oracle-based Laboratory Information Management System project management with barcode interface.
- Mining of existing SNP databases using the SNPselector program
- Compilation of local SNP database resources for SNP projects
- Mouse tail genotyping
- SNP genotyping
- Gene re-sequencing

The room was filled with scientists interested in MGC services. (Photo courtesy of Steve McCaw)

The audience was clearly receptive to the new service and eager to begin using the facility. Except for a few comments about redundant bar coding — labs that already use barcodes will still need to identify their samples with Core stickers — most of the scientists, including one especially impatient staff scientist, Dmitry Gordenin, Ph.D., couldn't wait to get started.

A few scientists queried Burch about how the facility will handle the mass of data it will be generating when labs begin taking full advantage of the new resources. Several seemed to share the sentiments of Senior Scientist Darryl Zeldin, M.D., who predicted that demand would be "substantially higher" than the 20 strains each week that Burch and the committee are anticipating at startup. However, Bell said, "I believe that we can eventually handle genotyping on several hundred mouse strains per week."

There will be a series of smaller meetings in October to work out more details about the Core. "This is really an experiment," added Acting Scientific Director Perry Blackshear, M.D., D.Phil. "Nothing is fixed. If demand outstrips the supply, we'll increase the Core as needed."

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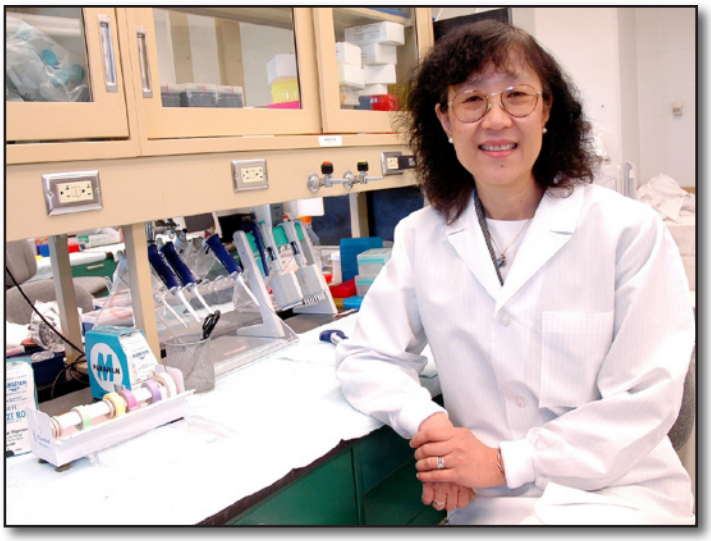
Endocrine Disruptor Conference — Epigenetic Outcomes

By Eddy Ball

On August 28, NIEHS grantee Shuk Mei Ho, Ph.D., reported recent data related to the "epigenetic reprogramming" that can result from exposures to endocrine disrupting compounds (EDCs) during critical periods of life. Her talk, "Epigenetics for the Toxicologist and Epidemiologist," was a featured presentation during the meeting "Future Research on Endocrine Disruption: Translation of Basic and Animal Research to Understand Human Disease" held August 27-29 at the Marriott at the Civic Center in Durham, N.C.



NIEHS grantee Shuk Mei Ho (Photo courtesy of the University of Cincinnati)

A professor and chair in the Department of Environmental Health at the University of Cincinnati Medical School, Ho developed an emerging theme in the area of EDC research, the application of epigenetics to epidemiological studies. Specifically, Ho looked at the influence of early life EDC exposure on later human development.

"Epigenetics is very dynamic and actually changes over time during your entire life span," Ho told her audience. "There are some critical periods that are important, for example, the embryonic stage, early childhood, the time of puberty and also advanced age (relaxation of the epigenome)."

The epigenetic changes taking place in these developmental windows, she continued, are heritable modifications that potentially trigger trans-generational effects of exposures. At the same time, however, these bi-directional changes are reversible — and potential targets for interventions.

By exploring these potentially heritable traits, Ho addressed two of the important challenges of EDC research — the role of multiple exposures at various developmental stages and the trans-generational effects of exposure to EDCs. Ho also highlighted a point of convergence between EDC research and the new NIH Roadmap 1.5 Epigenetics Initiative now underway, positioning EDC investigations within an area of robust research activity at NIEHS.

"The epigenome serves as an interface between the dynamic environment and the inherited static genome," Ho explained, influencing what set of genes will be expressed and what genes will remain silent. For example, one of the target genes in her animal studies, which is responsible for encoding the enzyme phosphodiesterase 4 (*PDE4D4*), is normally silenced in adult animals. In research performed with Gail Prins, Ph.D., at the University of Illinois at Chicago, Ho determined that the gene is over-expressed in animals treated with estrogen or the EDC Bisphenol A during fetal development.

When exposed to a hormonal challenge later in life, these animals were more likely to have increased levels of prostate-specific antigen. They were also more likely to develop prostate cancer than those not exposed during development. Estrogens and EDCs are thus capable of reprogramming the organism in early life by interfering with the normal DNA methylation pattern that gradually silences *PDE4D4* during aging.

Translating the results of toxicology studies in animal models to the investigation of human diseases, Ho studied the effects of estrogens on the higher incidence of prostate cancers among African American men. Caucasian women, she noted, tend to have lower estrogen levels during pregnancy than do African American women. Ho hypothesized that the sons of African American women would have a greater likelihood of developing cancer decades later due to higher neonatal exposures to estrogen. This theory has expanded the view of a "born with" genetically determined risk of disease to a new paradigm that environmentally induced reprogramming of disease-related epigenomes continues to modify disease risk and development long after birth.

Methylation-sensitive polymerase chain reaction (PCR) studies of prostate normal epithelia cells micro-dissected from a group of 35 prostate cancer patients showed a marked reduction in methylation status in samples from African American males and a significant over-expression of *PDE4D4*. This race-specific estrogen exposure in fetal development may parallel the animal model and induce mother-to-offspring impacts on later life risk for prostate cancer.

According to Ho, extrapolation of these preliminary findings to EDC exposure raises concerns about *in utero* exposure to ED contaminants in food and drinking water.

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Oceanographer Reports on "Red Tide" in the Gulf of Maine

By Eddy Ball

Woods Hole Oceanographic Institute (WHOI) Senior Scientist Donald Anderson, Ph.D., was the featured speaker in the NIEHS Frontiers in Environmental Sciences Lecture Series on August 31 in Rodbell Auditorium. Hosted by Fred Tyson, Ph.D., Anderson's lecture was titled "Don't Eat the Clams: Managing the Threat from the New England Red Tide."

Along with his work as a marine biologist at Woods Hole, Anderson is the director of the WHOI Coastal Ocean Institution and the U.S. National Office for Marine Biotoxins and Harmful Algal Blooms (HABs). He is also one of the lead investigators at the Woods Hole Center for Oceans and Human Health, which is jointly funded by the NIEHS Centers for Oceans and Human Health and the National Science Foundation (NSF).

According to Anderson, Alexandrium is self-seeding, replenishing the cyst population and expanding nesting beds every summer. (Photo courtesy of Steve McCaw)

For much of his career, Anderson has focused on the natural phenomenon of cyclical HAB outbreaks along the New England coast. A 2005 outbreak in that region of the species of *Alexandrium* that secretes Paralytic Shellfish Poisoning (PSP) inducing toxins endangered the lives of several careless fishermen and resulted in a $50 million loss to the Massachusetts fishing industry.

Anderson's efforts are directed at understanding the life cycles of these HABs and developing hydrodynamic conceptual models to help predict the outbreaks of what is popularly known as the New England "red tide." "The term 'red tide' is misleading," he explained, because in fact many harmless organisms can produce the

characteristic red tint, while water containing several of the most harmful species retains its natural color.

"It's a problem where shellfish have filtered several types of algae from the water as food and accumulated that toxin to dangerous levels," Anderson said. "The most widespread of all of the HABs, it [PSP] is virtually everywhere" in the world's coastal environments. At high enough concentrations, he noted, "If anyone in this room ate two or three clams [containing the very stable poison saxotoxin that is produced by *Alexandrium*], it would be lethal."

Host Fred Tyson is a program administrator in the Susceptibility and Population Health Branch of the Division of Extramural Research and Training (DERT), which administers grants to the Oceans and Human Health Centers. (Photo courtesy of Steve McCaw)

Investigations into the life cycle of *Alexandrium* from cyst to bloom have taken Anderson into the nesting beds off the coast of Nova Scotia in the Bay of Fundy, along the coasts of Maine, New Hampshire and Massachusetts where coastal currents and storms spread the organisms as far south as Martha's Vineyard, and, most recently, into the international waters of Georges Bank.

Anderson maintained his audience's interest with his account of unraveling the mysteries surrounding HABs. His talk kept some people, such as Tyson's colleague DERT Program Analyst Liam O'Fallon, literally on the edge of their seats. (Photo courtesy of Steve McCaw)

Georges Bank is a comparatively shallow fishing area along the coastal shelf 120 kilometers off the coast of Massachusetts. Although its rich sources of cod and other species have declined, Georges Bank is still a $100 million annual shellfish resource where high concentrations of the organism now are flourishing. These fishing grounds, Anderson explained, may turn out to pose a significant human health threat if HAB populations increase as predicted — and create a regulatory nightmare for states on the New England and even Mid-Atlantic coasts.

Until recently, record keeping of the outbreaks was spotty. Thanks to work by Anderson's group and other researchers, analysis of data from the past three decades has become much more sophisticated with improved models. New technology, including the Environmental Sampling Processor robot armed with DNA and small-unit RNA probe arrays, promises to increase real-time data gathering on specific HAB populations for more accurate forecasting.

Unfortunately, even as prevalence worldwide increases, Anderson observed, "There are still more questions here than answers." There is considerable victim variability, and scientists have been unable to predict how much non-indigenous seeding is taking place in such places as Georges Bank. Also, the organism is "made for survival" with a cyst viability rate of 50 percent after five years — and some cysts may remain viable for up to 30 years.

"I want to emphasize that this partnership between NIEHS and NSF is so timely and so important," Anderson concluded, "because it's bridging this gap between this human health problem and the oceanography involved."

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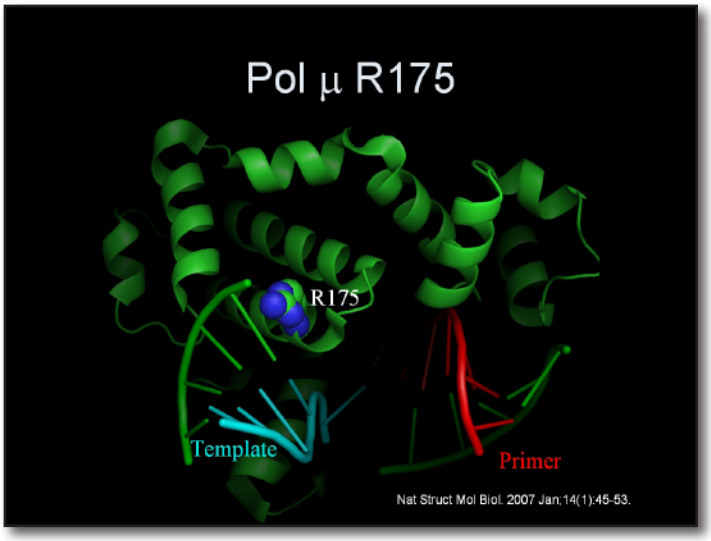
Dissecting the Complexities of NHEJ in DNA Repair

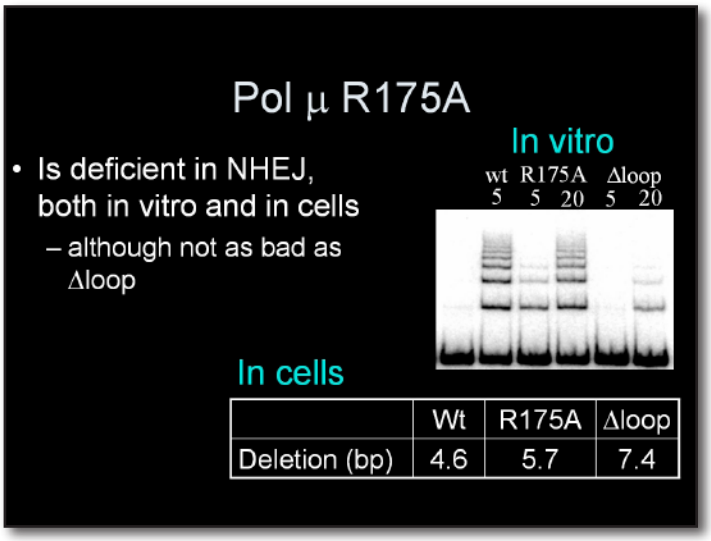
By Robin Arnette

During a visit to NIEHS on September 12, Dale Ramsden, Ph.D., associate professor in the Department of Biochemistry and Biophysics and the Lineberger Comprehensive Cancer Center at the University of North Carolina at Chapel Hill School of Medicine, spoke to a standing-room only audience in F193 in the Rall building. His seminar, "Nonhomologous End Joining and Base Excision Repair: Brothers from Another Mother," discussed some of the findings of his work. Robert London, Ph.D., head of the Nuclear Magnetic Resonance Group in the NIEHS Laboratory of Structural Biology, hosted the event.



Robert London, Ph.D., Lars Pedersen, Ph.D., and Thomas Kunkel, Ph.D., members of the NIEHS Laboratory of Structural Biology, collaborated with Ramsden to generate a computer model of the amino acid in loop 1 of pol μ (R175) that interacts with DNA. (Graphic courtesy of Dale Ramsden)

Ramsden began his seminar with an overview of DNA repair. During a single strand break, several mechanisms, such as nucleotide excision repair and base excision repair, lead to accurate repair of the damage. "But when you have a double-strand break caused by ionizing radiation, there are actually two ways to fix it: homologous recombination (HR) or nonhomologous end joining (NHEJ)," Ramsden explained. In HR the ligation of broken ends requires a homologous sequence or template to guide repair, but in NHEJ no such template is needed.



Ramsden used site-directed mutagenesis to change the arginine in pol μ to an alanine (R175A). Both in vitro and in vivo results indicated that the mutant pol μ is deficient in NHEJ and therefore requires a DNA template when promoting end joining. (Graphic courtesy of Dale Ramsden)

Ramsden went on to explain that in eukaryotes several core factors are required for NHEJ. One of the factors, DNA Ku protein, exists as a heterodimer of Ku70 and Ku80 and recruits the catalytic subunit of DNA protein kinase (DNA-PKcs). DNA ligase IV and XRCC4 are also required, but Ramsden found in his studies that the protein XLF, also known as Cernunnos, promoted synaptic maintenance and allowed the Ku–XRCC4–ligase IV complex to join mismatched ends directly.

During the second portion of the talk Ramsden discussed the interactions between DNA polymerases—deoxynucleotide transferase (TdT), pol μ and pol λ—in NHEJ. He knew from research done in other labs that TdT was template-independent, but he wanted to know if that held true for pol μ and pol λ. Using an *in vitro* assay Ramsden measured the activity of pol μ and pol λ by adding them separately into solution that either contained or lacked the Ku–XRCC4–ligase IV template. In the presence of the template both polymerases ligated the ends and extended the primer, but in the absence of template, pol λ lacked activity. This suggested that pol μ was template-independent like TdT.

To find out what part of pol μ was involved in binding and extending DNA, he turned to structural data. Ramsden's NIEHS collaborators, including London, Lars Pedersen, Ph.D. and Thomas Kunkel, Ph.D., generated computer models and more recently a structure that not only indicated that loop 1 in pol μ had a similar structure to loop 1 in TdT, polβ and pol λ, but they also identified additional requirements for pol μ's activity. This included an arginine at amino acid position 175 (pol μ R175) which interacts with the end containing DNA template. Ramsden used site-directed mutagenesis to change the arginine to alanine (pol μ R175A). It turned out that although the mutant pol μ R175A has wild type TdT-like template-independent activity, it is template-dependent when it comes to promoting end joining.

Ramsden's research into determining the exact mechanism and the players that are involved in NHEJ are important because cells suffer double-strand breaks on an almost daily basis. If this damage isn't fixed, it can lead to cell death or cancer.

The one take home message Ramsden wanted to convey was simple. "The pathway that I work on [non-homologous end joining] is far more sophisticated in making accurate junctions than we would have expected," he said. "We commonly think of this as an error-prone pathway, but it is a lot more precise than it looked initially."

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Andrew Marks to Speak October 9

By Eddy Ball

The 2007-2008 NIEHS Distinguished Lecture Series will continue on October 9 with a talk by Andrew Marks, M.D., at 11:00 a.m in Rodbell Auditorium. Marks will speak on "Defective Calcium Regulation as a Cause of Heart Failure and Sudden Cardiac Death.

Distinguished Lecturer Andrew Marks (Photo courtesy of Columbia University)

Marks is a professor and chair of the Department of Physiology and Cellular Biophysics at the Columbia University College of Physicians and Surgeons. He also serves as the director of the Center for Molecular Cardiology.

Using a variety of techniques including molecular biology, biophysics, cell biology, imaging and structural biology, Marks' laboratory studies the mechanisms that regulate muscle contraction. He and his group are especially interested in understanding better the regulation of calcium release channels on the sarcoplasmic reticulum that control excitation-contraction (EC) coupling in cardiac and skeletal muscle.

The lab has developed a number of genetic mouse models (primarily knock-ins and knock-outs) to provide insights into the regulation of key signaling pathways that control muscle contraction. Marks' group has also tested novel therapeutic approaches, including those that fix the "leak" in the RyR2 calcium release channel that causes heart failure and sudden cardiac death

Marks' lecture will be hosted by Pharmacologist Jim Putney, Ph.D., head of the Calcium Regulation Group in the Laboratory of Signal Transduction.

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Extramural Update

The National Institute of Environmental Health Sciences has issued a Funding Opportunity Announcement for its Outstanding New Environmental Science (ONES) award, a highly successful program of R01 research grants specifically for new investigators.

The Outstanding New Environmental Science Award is designed to identify outstanding scientists in the early, formative stages of their career who intend to make a long term career commitment to research in the mission area of the NIEHS, but have not yet successfully competed for their first R01 grant support. Applications are sought that propose highly innovative research programs focusing on problems of environmental exposures and human biology, human pathophysiology and human disease.

This is the third year the program has been announced. In the first two years of the program, 15 grant awards were made.

Applications will be accepted for up to $400,000 in direct costs for years 1-2, with up to $275,000 in years 3-5. This includes up to $150,000 per year for equipment or other resource development in years 1-2.

The program is designed to be highly competitive. To encourage universities to identify their best new investigators as potential applicants, only one application per school or college within an institution will be accepted.

Letters of intent for this initiative are due November 13, 2007, with applications due on December 10, 2007.

For the full text of the announcement, please refer to the NIH Guide for Grants and Contracts at: http://grants.nih.gov/grants/guide/rfa-files/RFA-ES-07-005.html.

Program Contact: Dr. Carol Shreffler (Shreffl1@niehs.nih.gov)

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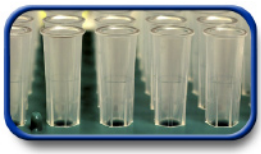

Intramural Papers of the Month

By Robin Arnette

Susceptibility to Human Acute Lung Injury

The transcription factor, NRF2, confers protection against oxidant injury, but mutations in the gene may help identify patients who are susceptible to oxidant-induced acute lung injury (ALI). The results were published in *The FASEB Journal* by a team of scientists from NIEHS, the University of Pennsylvania School of Medicine, Johns Hopkins Bloomberg School of Public Health, Children's Hospital of Philadelphia and the University of Tsukuba.

The researchers used a positional cloning approach to identify *Nrf2* as a susceptibility gene in inbred mice, and then sequenced *NRF2* in four ethnically diverse human populations. They identified six novel single nucleotide polymorphisms (SNPs) in *NRF2*, and one of these, –617 (C/A), significantly affected basal

NRF2 expression and function. They then asked whether functional *NRF2* SNPs associated with ALI in a prospective cohort of patients with major trauma. Compared to trauma patients with normal *NRF2*, those trauma patients with a –617 A SNP had a 6-fold higher risk of developing ALI.

This translational investigation provides novel insight into the molecular mechanisms of susceptibility to ALI, and may help to identify patients who are predisposed to develop ALI under at-risk conditions, and other oxidative stress-related illnesses.

Citation: Marzec JM, Christie JD, Reddy SP, Jedlicka AE, Vuong H, Lanken PN, Aplenc R, Yamamoto T, Yamamoto M, Cho H-Y, Kleeberger, SR. 2007. Functional polymorphisms in the transcription factor NRF2 in humans increase the risk of acute lung injury. FASEB J 21(9):2237-2246.

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Activation-induced Deaminase Deficiency Prevents Lupus Symptoms in Mice

In an NIEHS-funded study published in *The Journal of Immunology*, scientists from NIEHS and Pathology Associates reported new findings related to systemic lupus erythematosus. Their investigation showed that a strain of mice that usually develop many characteristics of human form of the disease don't develop symptoms if a key gene is removed. The results are an important step in the fight against lupus, which affects an estimated 1.5 million Americans.

MRL/lpr mice generally develop kidney disease, secrete hypermutated autoantibodies and have enlarged spleens and lymph nodes as do humans with lupus, but MRL/lpr mice that lack the activation-induced deaminase (AID) gene experienced a significant decrease in the aforementioned symptoms and exhibited increased survival rates. Most importantly, however, these mice contain high serum levels of autoreactive, unmutated IgM antibodies and fully functioning B cells.

The researchers theorized that since the AID-deficient MRL/lpr mice were unable to undergo somatic hypermutation (SHM) and isotype class switch recombination (CSR)— two programmed processes that occur during an immune response—IgM-bearing B cells accumulated and conferred some protection against lupus-like symptoms.

Citation: Jiang C, Foley J, Clayton N, Kissling G, Jokinen M, Herbert R, Diaz M. 2007. Abrogation of lupus nephritis in activation-induced deaminase-deficient MRL/lpr mice. J Immunol 178(11):7422-7431.

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The Involvement of p38 MAPK and Hsp27 in Bronchiolitis

In an NIEHS-funded study published in the *American Journal of Physiology-Lung Cellular and Molecular Physiology*, researchers from the Laboratory of Respiratory Biology reported that they were able to pinpoint how changes in endothelial and epithelial membrane integrity led to fluid build-up in the lungs of children, the elderly and immuno-compromised patients with bronchiolitis.

The respiratory syncytial virus (RSV) is a negatively-stranded non-segmented RNA virus and is the major cause of bronchiolitis. The researchers infected primary human bronchial epithelial and A549 human alveolar epithelial cells with RSV. They measured the cells' permeability, also known as trans-epithelial resistance (TEpR), using an electrical cell-substrate impedance sensing system. They detected a decrease in TEpR five to ten hours after the infection and a continued 30 percent decrease over time.

Since earlier data from these researchers and others have shown that the MAPK pathway was involved in endothelial permeability, they treated cells with a variety of MAPK protein inhibitors and performed Western blots looking at the phosphorylation of Hsp27, a 27kDa heat shock protein. Their research indicated that the decrease in TEpR could be weakened by using p38 MAPK inhibitors, but a decrease in TEpR also corresponded to an increase in Hsp27 phosphorylation and actin microfilament rearrangement. This is the first report to detail the mechanism of fluid build-up in bronchiolitis.

Citation: Singh D, McCann KL, Imani F. 2007. MAPK and heat shock protein 27 activation are associated with respiratory syncytial virus induction of human bronchial epithelial monolayer disruption. Am J Physiol Lung Cell Mol Physiol 293(2):L436-L445.

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DNA Replication Fidelity-Active Site is Conserved in Yeast

Researchers from NIEHS in collaboration with investigators from Umeå University in Sweden have determined that the methionine at position 644 (M644) within the yeast DNA polymerase ε (pol ε) active site plays an important role in replication fidelity. The findings were published in *Nucleic Acids Research*.

Earlier sequence identity studies revealed that M644 in pol ε corresponded to similar active site positions in other *Saccharomyces cerevisiae* polymerases such as T4 pol, pol α and pol δ. They also knew that the side chain of M644 specifically interacted with a tyrosine that contacts the sugar of the incoming dNTP. Therefore, the research team used site-directed mutagenesis to replace the M644 with leucine (M644L), tryptophan (M644W) and phenylalanine (M644F).

They discovered that M644L and M644W correctly synthesized DNA (high fidelity), but that M644F had significantly increased replication errors (low fidelity). The team theorized that the aromatic ring present in the amino acid phenylalanine possibly altered the conformation of the binding pocket, leading the M644F mutant pol ε to insert the wrong nucleotides. The data from this project and others indicated that the position occupied by M644 in pol ε is an important determinant of replication fidelity in all three B family polymerases.

Enzymes with amino acid replacements at this position are being used to probe the roles of the B family polymerases in leading and lagging strand replication of normal DNA, as well as in replication of DNA that has been damaged as a result of environmental stress.

Citation: Pursell ZF, Isoz I, Lundström E-B, Johansson, Kunkel TA. 2007. Regulation of B family DNA polymerase fidelity by a conserved active site residue: characterization of M644W, M644L and M644F mutants of yeast DNA polymerase ε. Nucleic Acids Res 35(9):3076-3086.

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Extramural Papers of the Month

By Jerry Phelps

Supplementation Counteracts Bisphenol A-Induced Epigenetics Changes

Recent research by NIEHS grantee Randy Jirtle and his research team shows that epigenetic changes induced by bisphenol A lead to problems with fertility and breast and prostate cancer in rat pups whose mothers were fed the compound in their diets. In addition, the team found that maternal dietary supplementation with folic acid or genestein reversed the epigenetic effects in the offspring.

Bisphenol A is a compound found in many types of plastic products including water and soft drink bottles, the liners of metal food cans, dental sealants, adhesives and many other plastics that humans come in contact with. Over time, small amounts of the compound leach out of the containers and into the food or beverage. Previous research has established that bisphenol A causes epigenetic changes through hypomethylation.

The Jirtle lab showed that epigenetic patterning during early stem cell development is sensitive to bisphenol A exposure. The addition of either methyl donor, folic acid or genestein, stopped the hypomethylating effect of bisphenol A. The authors conclude that their study's results support the inclusion of epigenetic effects of chemicals into risk assessments. The study also supports further investigation into possible dietary supplements that might counteract the adverse effects of environmental agents on the epigenome.

Citation: Dolinoy DC, Huang D, Jirtle RL. 2007. Maternal nutrient supplementation counteracts bisphenol A-induced DNA hypomethylation in early development. Proc Natl Acad Sci U S A. 2007 104(32):13056-61.

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Loss of Norepinephrine Causes Parkinson-Like Tremor in Mice

Parkinson's disease is a chronic neurodegenerative disease that is characterized by the loss of dopamine-producing neurons in the substantia nigra region of the brain. There is also a simultaneous loss of norepinephrine-producing neurons in a region called the locus coeruleus. Administration of methyl phenyl tetrahydropyridine (MPTP) to laboratory animals is a common model for Parkinson's disease; however, MPTP does not cause the motor deficits seen in humans with Parkinson's disease.

NIEHS-supported investigators tested mice to determine whether the loss of norepinephrine neurons was necessary for the motor deficits seen in Parkinson's disease. They used transgenic mice that totally lack norepinephrine altogether.

The researchers detected no motor deficits in control mice treated with MPTP — despite an 80 percent reduction in the number of dopamine-producing cells. On the other hand, the norepinephrine-lacking mice exhibited motor deficits in most tests, along with other movement disorders, despite having normal dopamine levels. The researchers were able to reverse the motor effects by supplementation with a norepinephrine precursor and determined that increased levels of norepinephrine protected dopamine-producing neurons from MPTP toxicity.

This study suggests that loss of locus coeruleus neurons contributes to the motor deficits seen in Parkinson's disease and implies that administration of norepinephrine-like drugs could have dual therapeutic effects.

Citation: Rommelfanger KS, Edwards GL, Freeman KG, Liles LC, Miller GW, Weinshenker D. 2007. Norepinephrine loss produces more profound motor deficits than MPTP treatment in mice. Proc Natl Acad Sci U S A. 104(34):13804-13809.

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VEGF Polymorphisms Associated with Higher Mortality in ARDS

Endothelial cell injury is an important factor in predicting the outcome of patients with acute respiratory distress syndrome (ARDS), a lung injury characterized by damage to the alveoli and increased pulmonary vascular permeability. Vascular endothelial growth factor (VEGF) is known to play a critical role in endothelial cell death and angiogenesis.

David Christiani and colleagues at the Harvard School of Public Health investigated the impacts of polymorphisms in the *VEGF* gene on the clinical outcomes of ARDS. They found three variations of the gene in 1,253 intensive care patients with risk factors for ARDS; 394 of these patients later developed the syndrome. Two of the polymorphisms were associated with increased mortality from ARDS, with risk increased two to four fold. Plasma VEGF levels were significantly lower, by more than half, in patients with the two at-risk polymorphisms as compared to the other gene variation.

The research team pointed out that this is a small study, which needs to be replicated, along with studying other functional *VEGF* variations before any definitive conclusions can be made. However, they concluded that at least two *VEGF* polymorphisms are associated with increased mortality from ARDS and that their findings may lead to the discovery of new treatments for ARDS.

Citation: Zhai R, Gong MN, Zhou W, Thompson TB, Kraft P, Su L, Christiani DC. 2007. Genotypes and haplotypes of the VEGF gene are associated with higher mortality and lower VEGF plasma levels in patients with ARDS. Thorax 62(8):718-722.

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Chromatin Remodeling Complex and DNA Damage Checkpoint Responses

NIEHS-supported scientists at the University of Texas M. D. Anderson Cancer Center have found that a signaling pathway and a chromatin remodeling pathway interact in response to DNA damage. The team suggests that this finding could open an entirely new category of targets for attacking cancer.

In response to DNA damage, checkpoint genes temporarily halt cellular division while DNA repair genes mobilize. The ATM/ATR kinases are known to regulate DNA repair and checkpoint pathways by phosphorylating other proteins involved in DNA damage control. The group found that one of these phosphorylated proteins is a subunit of the chromatin remodeling complex called INO80. Additional experiments showed that the activated protein regulates checkpoint pathways, but not DNA repair pathways.

Chromatin remodeling results in greater access to DNA so that repair machinery can attach and fix the damaged DNA strands. The team discovered that the les4 subunit of the INO80 remodeling complex is activated by the ATM/ATR kinases, a necessary step for certain cellular checkpoints to work properly. Mutation of les4 phosphorylation sites did not significantly affect DNA repair processes, but did influence DNA damage checkpoint responses. These findings establish the chromatin remodeling complex and a component in the DNA damage signaling pathway that controls checkpoint responses.

Citation: Morrison AJ, Kim JA, Person MD, Highland J, Xiao J, Wehr TS, Hensley S, Bao Y, Shen J, Collins SR, Weissman JS, Delrow J, Krogan NJ, Haber JE, Shen X. 2007. Mec1/Tel1 phosphorylation of the INO80 chromatin remodeling complex influences DNA damage checkpoint responses. Cell 130(3):499-511.

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