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June 2009

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Science Notebook

Nobel Laureate Examines Immune Cell Deviations

Lymphoma is a term used to describe a group of cancers that affect lymphocytes — the cells involved in the immune system. Pathologists who view these cancerous lymphocytes under a microscope usually see one type of cell, but sometimes two different cell types exist in the same sample. ...read more

Birnbaum is Plenary Lecturer at BFR2009

NIEHS and National Toxicology Program (NTP) Director Linda Birnbaum, Ph.D., was back on very familiar turf when she delivered a plenary lecture at the 11th Annual Workshop on Brominated Flame Retardants (BFR2009) held May 19–20 at the Government Conference Centre in Ottawa. ...read more

Guest Lecturer Offers New Insight into Heritable Epigenetic Changes

Christophe Herman, Ph.D., a professor in the Department of Molecular and Human Genetics at Baylor College of Medicine, gave the latest talk in the NIEHS Laboratory of Molecular Genetics (LMG) Fellows Invited Lecture Series on May 18. ....read more

Seminar Highlights a Promising HIV Inhibitor

Structural biologists use techniques such as X-ray crystallography, mass spectrometry and nuclear magnetic resonance (NMR) to determine the structure and function of molecules.. ....read more

NIEHS Spotlight

Umbach Honored by American Statistical Association

In the world of biostatistics, there is probably no higher honor than the one to be given NIEHS Biostatistics Branch (BB) Staff Scientist David Umbach, Ph.D., by the American Statistical Association (ASA). ...read more

Children's Center Research Highlighted at Pediatric Meeting

This year, NIEHS enjoyed a higher profile at the world's premier gathering of pediatric professionals — the Pediatric Academic Societies (PAS) Annual Meeting May 2–5 in Baltimore. ...read more

Hrynkow Represents NIEHS at AAAS Forum

Continuing her work in forging partnerships and cross-disciplinary collaborations in global environmental health, NIEHS Associate Director Sharon Hrynkow, Ph.D., organized and chaired a panel discussion on the linked issues of climate, energy and health at the 2009 AAAS Forum on Science Technology and Policy. ....read more

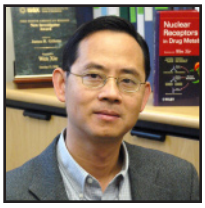
NIEHS Supporting Greenhouse Gas Emissions Study Group

NIEHS Associate Director Chris Portier, Ph.D., has the lead role for NIEHS on an international team of scientists investigating the potential health benefits of reducing greenhouse gas emissions to help combat climate change. ...read more

Clinical Research Unit Ribbon Cutting July 27

NIEHS will cut the ribbon on its new Clinical Research Unit (CRU) before an audience of scientists and distinguished visitors on July 27 at its Research Triangle Park, NC campus. ....read more

Science Notebook



Xie Explores Hormone Regulation by Nuclear Receptors

On April 30, Wen Xie, M.D., Ph.D., presented a seminar at NIEHS on "Nuclear Receptor-Mediated Gene Regulation in Hormonal Homeostasis" as part of the NIEHS Laboratory of Pharmacology (LP) and Laboratory of Molecular Toxicology Seminar Series.. ...read more

Research Finds Novel Roles for AhR in Development

A recent study reports on novel roles for the cellular environmental sensor aryl hydrocarbon receptor (AHR). ...read more

Well Water Should Be Tested Annually to Reduce Health Risks to Children

Private well water should be tested yearly, and in some cases more often, according to new guidance offered by the American Academy of Pediatrics (AAP). ...read more

Possible Link Between Childhood Obesity and Allergies

A new study indicates there may be yet another reason to reduce childhood obesity — it may help prevent allergies. ...read more

Expert Panel Reviews New Local Lymph Node Assay for Product Testing

An international scientific peer review panel of 15 expert scientists met on April 28-29 on the NIH Bethesda campus to review new test methods proposed to determine if chemicals and substances may cause allergic contact dermatitis. ...read more

NIEHS Spotlight

NIEHS Participates in New One Health Initiative

Long before news about the H1N1 "swine flu" virus concerned people around the world, leaders in the animal health community were already organizing to better understand and deal with the growing health threat posed by multi-host pathogens. ....read more

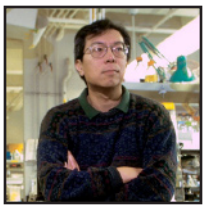
EPA Leader Reports on Progress in Toxicity Testing

Robert Kavlock, Ph.D., visited NIEHS on May 7 to present a status report on the ToxCast™ program he oversees as the director of the National Center for Computational Toxicology (NCCT) at the U.S. Environmental Protection Agency (EPA). ...read more

Tinkle Represents NIEHS and NIH at Drug Conference

NIEHS Senior Science Advisor Sally Tinkle, Ph.D., spoke at the Fourth Annual Chapel Hill Drug Conference May 13–14 at the University of North Carolina at Chapel Hill. ....read more

Inside the Institute



Scientific Leader Robert Tjian Speaks at NIH Asian Heritage Event

NIEHS staff were part of the off-site audience as NIH videocast its 2009 Asian/Pacific Islander Heritage Month Observance Program held May 14 in Masur Auditorium on the Bethesda campus. ...read more

Employees Pitch In with Habitat for Humanity Project

Continuing a tradition of community involvement with the non-profit group Habitat for Humanity, members of the NIEHS Division of Extramural Research and Training (DERT) Community Builders group donated an afternoon of their free time ... ...read more

Science Notebook

This Month in EHP

The June 2009 issue of *Environmental Health Perspectives* is now available online, with a feature story on the growing problem of antibiotic resistance and the emergence of new strains of bacteria. The journal also takes a critical look at the aquaculture industry's impact on the environment as increasing demand for fish leads to the proliferation of fish farms. ...read more

Upcoming Distinguished Lecturer Harinder Singh

NIEHS will welcome the next speaker in its 2008-2009 Distinguished Lecture Series on June 9 at 11:00 in Rodbell Auditorium. ...read more

ATS Calls for 2010 Conference Proposals

The American Thoracic Society (ATS) has announced a "Call for Input" for planning the program of its international conference, ATS 2010, scheduled May 14–19, 2010 in New Orleans. ...read more

Extramural Research

Extramural Update

In April 2009 the NIEHS Superfund Research Program (SRP) announced three new multi-year program grant awards: Brown University, the University of Washington (UW) and Oregon State University (OSU). Each of these grants is comprised of complementary projects, which are thematically related around an environmental health hazard of interest. ...read more

Intramural Research

Intramural Papers of the Month

- Urate May Protect Against Parkinson's Disease
- Cholesterol-Rich Microdomains Play Crucial Role in MEK-ERK Pathway
- SIRT1 May Prevent Obesity-Associated Diseases
- A New Algorithm for Protein Binding Site Analysis

Extramural Research

Extramural Papers of the Month

- Alzheimer's Disease Linked to Mitochondrial Damage
- Swine Flu Susceptibility Linked to Arsenic Exposure
- Gene May Be Linked to Lung Cancer
- Phthalate Exposure May Extend Pregnancy

Calendar of Upcoming Events

- **May 31–June 3 (Offsite Event)**, at the U.S. Environmental Protection Agency in RTP, 9:00–6:00 — 11th International Congress on Combustion By-Products and Their Health Effects
- **June 1**, in Rall F-193, 2:00–3:00 — Laboratory of Neurobiology Seminar Series with Pavel Ortinsky, Ph.D., speaking on "Astrogliosis impairs inhibitory synaptic signaling in the mouse hippocampus"
- **June 2**, in Rodbell Auditorium, 11:00–12:00 — Biostatistics Branch Seminar on "Using Mouse Gene Expression and Phenotypes to Explore the Effects of Atherogenic Diet" with Keith Shockley, Ph.D.
- **June 9**, in Rodbell Auditorium, 11:00–12:00 — Distinguished Lecture Seminar Series, featuring a talk by Harinder Singh, Ph.D., on "Gene Regulatory Networks Orchestrating Innate and Adaptive Immune Cell Fates"
- **June 17**, in Rodbell Auditorium, 11:00–12:00 — Summers of Discovery Seminar Series, speaker and topic TBA
- **June 18**, in Rall D-450, 11:00–12:00 — Laboratory of Reproductive and Development Toxicology Special Seminar with Evan Simpson, Ph.D., topic TBA
- **June 23**, in Rodbell Auditorium, 8:00–5:00 — Board of Scientific Counselors Review Meeting
- **June 24**, in Rodbell Auditorium, 11:00–12:00 — Summers of Discovery Seminar Series with Bill Schrader, Ph.D., addressing "Poster Presentation Skills" and "Computing Skills for Poster Session Presentation"
- **June 25–26 (Offsite Event)**, at the J.W. Marriott Resort and Spa in Las Vegas, 8:30–4:30 — 2009 NIH Regional Seminar on Program Funding and Grants Administration
- **June 25–26 (Offsite Event)**, at the Hilton Arlington in Arlington, Va., 8:30–5:00 — Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) meeting
- **July 1**, in Rodbell Auditorium, 11:00–12:00 — Summers of Discovery Seminar Series, with Thomas Kunkel, Ph.D., topic TBA
- View More Events: NIEHS Public Calendar

NIEHS Spotlight

Supplemental Funding and New Developments Dominate Council

By Eddy Ball

The NIEHS National Advisory Environmental Health Sciences Council (NAEHSC) gathered for its two-day spring meeting at NIEHS May 21–22. The group heard reports by leadership, shared their thoughts about future plans and initiatives, and grappled with what NIEHS and National Toxicology Program (NTP) Director Linda Birnbaum, Ph.D., described as the "moving target" of American Recovery and Reinvestment Act (ARRA) stimulus funding.

Birnbaum welcomed the Council's newest member, Johns Hopkins University oncologist Stephen Baylin, M.D., and introduced newly appointed NIEHS Acting Scientific Director John Pritchard, Ph.D., and NIEHS Acting Deputy Director Steve Kleeberger, Ph.D. (See related story)

NAEHSC Executive Secretary and Acting Director of the NIEHS Division of Extramural Research and Training (DERT) Gwen Collman, Ph.D., told members that along with continuing the practice of videocasting the event and making documents available online, NIEHS had advertised web access to members of the NIEHS extramural community — an extra effort to make proceedings as accessible as possible.

Birnbaum reviewed leadership and scientific developments since the Council's last meeting in February. She also highlighted NIEHS efforts toward "enhancing interactions with EPA" that are part of an initiative to strengthen existing partnerships and build new ones with sister institutes and centers and other government organizations with goals related to the NIEHS mission.

Turning to funding matters, Birnbaum told Council of her successful efforts to secure an additional $20 million in NIH ARRA stimulus funding for the NIEHS Superfund Research Program (SRP) and Worker Education Training Program (WETP). The additional allocation raised the total stimulus package for NIEHS to $187 million.

Like his colleagues, member Stephen Lloyd, Ph.D., found much to ponder as he listened to Collman's report on the ARRA stimulus funding initiative. "You guys are doing a phenomenal job with the onslaught, and it looks extraordinarily organized," he commented afterwards. (Photo courtesy of Steve McCaw)

Birnbaum was upbeat about the budget during her report and candid as members discussed stimulus funding later in the meeting. "This whole thing is rolling," she said. "You're going to get this stuff as quickly as it can be turned out." (Photo courtesy of Steve McCaw)

As she reviewed the Institute's budget for FY 2008 and 2009 and the President's request for 2010, Birnbaum said the figures show an increase of approximately 3.2 percent. If Congress accepts the recommendations for 2010, the total NIEHS budget will increase to $684 million in FY 2010, and the budget for SRP will grow at a smaller pace to $79 million.

Pritchard opened his report with news that sparked enthusiastic remarks from several members with ties to the academic community, where hiring has been sluggish at best —the Division of Intramural Research (DIR) program's search for six new principal investigators and the recent addition of Biostatistics Branch Tenure Track Investigator Raja Jothi, Ph.D. The news prompted Council member John Essigman, Ph.D., to comment that he was "heartened by the expansion of scientific expertise" in DIR.

Pritchard was followed by Acting Clinical Director Darryl Zeldin, M.D. who discussed plans for the NIEHS Clinical Research Center, which opens officially on July 27. These plans include pursuing accreditation from The Joint Commission (formerly JCAHO) during its second year of operation and creative partnerships with the NIH Clinical Center designed to maximize NIEHS funding for NIH clinical research efforts.

NTP Associate Director John Bucher, Ph.D., then reviewed the impact of his group's review of studies on bisphenol A and plans for expanded collaboration

Collman, left, retained the poise she showed above as she offered her best estimates of where and when NIEHS will spend its $187 million stimulus package. "I know it's May and we should know exactly what's on the table to choose from," she observed, "but we're still receiving applications." (Photo courtesy of Steve McCaw)

Council Hears Concept Clearance Presentations

Looking to the future of NIEHS research, DERT staff offered proposals for new directions in their programs:

- Breast Cancer and the Environment Research Centers (BCERC) — To continue support and to expand upon the BCERC, which is the only NIH project supporting trans-disciplinary research on the interaction of chemical, physical, biological, and social environmental factors with genetic factors using puberty as a window of susceptibility.

- Key Message Development and Dissemination Research Contract — To increase awareness of the role of the environment in breast cancer risk and the opportunities that life-style choices may make in modifying that risk through dissemination of expert-identified audience-sensitive key messages to breast cancer organizations and other targeted audiences.

- Engineered Tissue Systems for the Environmental Health Sciences — To foster the development of *in vitro* experimental and computational models replicating major organ systems to be used for increased throughput and high data content screening of the mechanistic and toxicological effects of potential environmental toxicants.

- Small Business Innovation Research (SBIR) Contract Studies — To allocate the legislatively mandated 2.5 percent of the NIEHS research and development budget to support small businesses via the SBIR program to develop tools to further research on eight topics identified as important for high-throughput screening development, toxicology research in the NIEHS WormTox program, sperm analysis and exposure to mold.

with the Food and Drug Administration. In the Report of the Executive Officer, NIEHS Associate Director for Management Marc Hollander showed Council members his group's draft Master Plan for infrastructure development at the NIEHS campus and described possible uses of two tracts for NIH facilities and a new data center.

The final leadership report by Collman offered members a behind-the-scenes look at how DERT administrators are tackling the ambiguities of stimulus funding priorities and the hundreds of applications that have already been received. As Collman explained, DERT has tried to anticipate application trends, developed internal controls to monitor conflict of interest and considered strategies for satisfying reporting requirements, including the number of jobs created, scientific impact and spending.

Pritchard joked about being one of the "gray beards" at NIEHS as he listed the new specialists he is recruiting to help the DIR program move forward into new areas of research. (Photo courtesy of Steve McCaw)

Collman explained that NIEHS is building a computer system, known as the NIEHS ARRA Supplements Operations System (SOS), to handle the flood of applications and proliferating number of decision-making documents. She also observed that the existing Electronic Council Concurrence protocol would need to be expanded to expedite approval of stimulus funding applications this summer.

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Standing Room Only at NIEHS Biomedical Career Day

By Eddy Ball

Ever since it debuted in 1997, the annual NIEHS Biomedical Career Fair has always been a timely and popular event, and the 2009 career fair on May 1 in the Research Triangle Park Environmental Protection Agency (EPA) conference center was no exception. Several sessions drew standing-room-only audiences, eager for insights into how they can succeed in an evolving job market, and, between sessions, the halls were packed with people establishing relationships that may one day help shape their careers.

According to members of the NIEHS Trainee Assembly (NTA), the 12th annual Biomedical Career Fair drew 267 students and trainees from the Triangle and beyond for a day filled with career development and networking opportunities. NIEHS Career Fair Committee co-chair Allison Schorzman, Ph.D., described the event as "the culmination of efforts by

The Career Fair worked like a well-oiled machine, and there were few signs of the hard work behind it, such as this conversation between Schorzman, left, and Industry-Big Pharma Panel moderator and NIEHS Epidemiology Branch Fellow Dana Hancock, Ph.D. (Photo courtesy of Steve McCaw)

several generations of trainees and generous support by the NIEHS Office of the Scientific Director and other public- and private-sector sponsors."

The program began with welcoming remarks by Schorzman, Harold Zenick, Ph.D., director of the National Health and Environmental Effects Research Laboratory in the EPA Office of Research and Development, and NIEHS Deputy Scientific Director William Schrader, Ph.D.

Keynote speaker Peter Fiske, M.B.A., Ph.D., set the tone for the day with his talk on "Putting Your Science to WORK: Practical Career Strategies for Young Scientists" (see text box). Fiske is chief technology officer for the venture-capital green-technology companies PAX Mixer, Inc. and PAX Water Technologies and author of the Sciencecareers.org monthly column "Opportunities" for the American Association for the Advancement of Science.

During the hours that followed Fiske's talk, attendees could choose from among three workshops and nine career-specific panel discussions. These sessions ranged from résumé/CV writing, presentation skills and government application tips to discussions of alternative opportunities for trainees in policy, teaching, entrepreneurship, communication, big pharmaceutical and other careers. Instructors, moderators and panelists included former NIEHS postdocs in various careers, government and educational professionals and people from various private sector companies with opportunities for people with Ph.D.s in science and technology.

Fiske flashed his winning smile several times during his engaging presentation. His charm and wit helped breathe new life into advice his audience may have heard several times before — but probably didn't find as relevant as when one of their own spoke from experience. (Photo courtesy of Steve McCaw)

Peter Fiske on the Ph.D. Career Quest

Fiske inspired his audience — and also kept them laughing through much of his talk — with the story he has told to several groups about the ups and downs of his own career-development odyssey. After receiving his doctorate in geophysics from Stanford University in 1996, Fiske's career path took him from a White House Fellowship in public policy at the Pentagon through a research position at Lawrence Livermore National Laboratories and an M.B.A. at the University of California, Berkeley to his current work in developing innovative, energy-efficient technology.

In the course of his talk, Fiske debunked stereotypes about Ph.D.s and conventional wisdom about the job-search process as he urged his listeners to reassess their skill sets. He flattered and cajoled, gave pointers for career development and networking, and offered insight into what employers really want in the successful applicant.

Fiske also introduced his 80/10/10 rule. "Spend 80 percent of your time on your job," he told his audience. Ten percent should be devoted to building networks with friends, family and colleagues — identifying the "friends of friends" who may be the connection a job seeker needs — and promoting professional accomplishments. He said the final ten percent should be spent in career development, becoming better versed both in the current job field and in areas that may be worth exploring in the future.

Among the many important messages he gave the audience was one of the simplest. Still, it takes a leap of faith for people who have invested an enormous amount of time and money in their scientific training to embrace it — only to find themselves question the goals they had pursued for so long. "If you don't like what you do for a living," he warned his listeners, "you probably won't be very good at it!"

Not surprisingly, networking, which is a stumbling block for many trainees and job seekers, was a theme that ran throughout the event. Schrader opened the meeting with an exercise in taking the initiative to meet new people, and participants could attend a networking lunch where they were strategically seated with session speakers. Between sessions and workshops, attendees could visit and mingle in the exhibits area where biomedical companies, government agencies and professional groups were on hand to offer information and a chance to meet people who just might be a link to an unexpected opportunity.

With a little serendipity and a lot of persistence, veterans of the NIEHS Career Fairs may one day look back on their experience there and join Fiske in saying, "Five years ago, I would never have predicted that I would end up here!"

"Networking" was the word of the day — a message that wasn't lost on Duke University Postdoctoral Fellow and Research Associate Ravi Metlapally, Ph.D. left. Metlapally spent some of his break time chatting with a representative of biotech company Athenix. (Photo courtesy of Steve McCaw)

Many of the workshops and sessions attracted standing-room-only crowds, including this workshop on résumé writing for non-academic jobs featuring Lori Conlan, Ph.D., of the NIH Office of Intramural Training and Education. (Photo courtesy of Steve McCaw)

Like his colleague in the Mass Spectrometry Group, NIEHS Fellow James Smedley, Ph.D., seemed to hang on Conlan's every word. (Photo courtesy of Steve McCaw)

NIEHS Mass Spectrometry Group Fellow Lake Paul, Ph.D., was eager to learn presentation strategies for putting his training in structural biology to work. (Photo courtesy of Steve McCaw)

Even science policy has its lighter side, as demonstrated by panelists EPA Congressional Liaison Jenny Noonan, left, and Sheila Newton, Ph.D., director of the NIEHS Office of Policy, Planning and Evaluation. (Photo courtesy of Steve McCaw)

Former NIEHS postdoc Eric Tien, Ph.D., center, laughed about common mistakes applicants can make in the world of Big Pharma. Shown, left to right, are panelists Elizabeth Roberts, D.V.M., Ph.D., of Novartis Animal Health U.S., Inc., Tien, Meg Ehm, Ph.D., of GlaxoSmithKline, and Robert Veneziale, Ph.D., of Shering-Plough. (Photo courtesy of Steve McCaw)

Although there was plenty of occasion for levity, attendees such as NIEHS Membrane Signaling Group Fellow Jody White, Ph.D., were also eager to get answers to their questions. (Photo courtesy of Steve McCaw)

At the end of the day, the organizing committee could take a well-deserved breather. Shown left to right are postdoctoral fellows Beth Oesterling-Owens (EPA), Omari Bandele (NIEHS), Jana Stone (NIEHS), Julie Hall (NIEHS), Schorzman (NIEHS), Patrick Brandt (formerly of NIEHS, now at UNC), Sophia Bolick (NIEHS), Shweta Trivedi (NIEHS), and Eva McLanahan (EPA). Not pictured were members Andres Cisneros (NIEHS), Suraj Dhungana (Enthalpy Analytical, formerly of NIEHS) and Dana Hancock (NIEHS). (Photo courtesy of Steve McCaw)

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Birnbaum Addresses Preparedness at WETP Meeting

By Eddy Ball

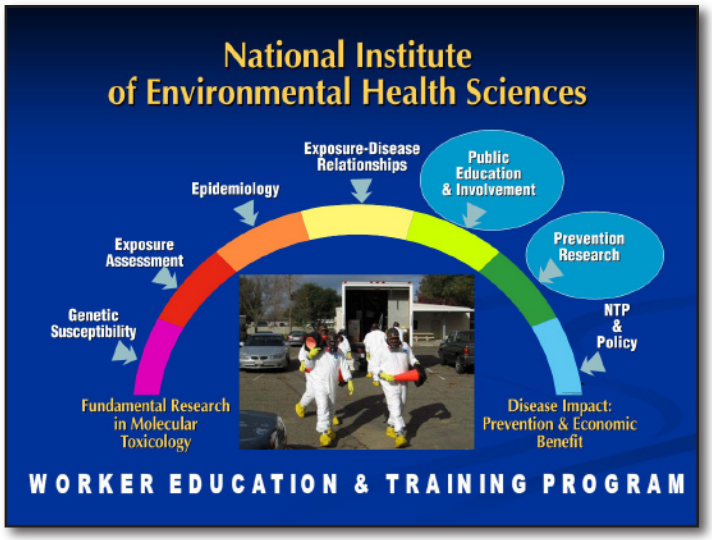
Director of the NIEHS and National Toxicology Program Linda Birnbaum, Ph.D., took her message of hope and challenge to the Spring 2009 Worker Education and Training Program (WETP) Awardees Meeting and Workshop April 29–May 1. She welcomed and acknowledged the grant awardees on April 29 and the next day spoke to the 150 attendees gathered at the Millennium Hotel in Cincinnati. The meeting culminated on May 1 with a Chemical Incident Scenario Exercise at the nearby Riverside Transit Center that offered participants and local organizations a chance to see training, innovations and preparation put into practice.

As Birnbaum described the accomplishments of WETP initiatives, she looked to future challenges, such as the emerging health threat posed by the H1N1 flu virus and global climate change. WETP is adapting its avian flu response program to help meet the needs of people responding to H1N1. (Photo courtesy of Steve McCaw)

Birnbaum expressed her support with her words and her engagement in workshop sessions, but she was unable to stay for the meeting's culminating event on May 1 — a Chemical Incident Scenario Exercise at the nearby Riverside Transit Center that offered participants and local organizations a chance to see training, innovations and preparation put into practice.

The workshop sessions and chemical spill exercise echoed the meeting's theme — "Local, State and Federal Partnerships for Chemical Preparedness and Response." The title of Birnbaum's keynote address on April 30 was "Moving Environmental Health Sciences Forward — Community Collaboration and Partnerships," which focused on the role of WETP within the NIEHS program structure.

Birnbaum joined WETP Director Chip Hughes, NIEHS Acting Director of Extramural Research and Training Gwen Collman, Ph.D., U.S. Environmental Protection Agency (EPA) Assistant Administrator Tim Fields, EPA Office of Emergency Management Director Debbie Dietrich and Federal Bureau of Investigation Intelligence Analyst Dennis Butler at the speakers' table.



Early in her keynote address, Birnbaum placed WETP at the center of the NIEHS research and translation umbrella with this visual representation.

In both her talks, Birnbaum stressed that the work of WETP principal investigators "on the front lines of environmental defense… is central to the NIEHS mission" of disease prevention and promotion of public health. She praised the program's network of partnerships and the fruitful collaborations that have made WETP preparedness and response efforts possible.

"You are an important part of the NIEHS family," Birnbaum assured her audience. "The qualities that I value in an organization apply directly to this cooperative relationship [fostered by WETP]

— open minds, respect for colleagues, divergent thinking, diversity, full disclosure, fairness, responsibility, accountability and a constructive, open environment that leads to genuine two-way communication." She lauded awardees for their work "where the rubber meets the road" in terms of the overall NIEHS mission of research translation from the bench to public health.

During her talk to awardees, Birnbaum outlined newly available administrative supplements made possible through the American Recovery and Reinvestment Act (ARRA). At the conclusion of her keynote address, where she reinforced her message of partnership and inclusion, Birnbaum returned to the Katrina response mantra that informs what WETP hopes to accomplish. "To be prepared against surprise is to be trained," read her closing slide. "To be prepared for surprise is to be educated."

NIEHS WETP and the Interstate Chemical Terrorism Workgroup (ICTW) co-sponsored the meeting and workshop. Created by the Superfund Amendments and Reauthorization Act of 1986, WETP funds through cooperative agreements non-profit organizations with a demonstrated track record of providing occupational safety and health education for development and delivery of high-quality training to workers involved in handling hazardous waste and responding to emergency releases of hazardous materials. ICTW, which was formed in 2002, is made up of public health, medical and emergency response professionals from all 50 states.

Behind the Scenes and on the Ground at the Riverside Transit Center

The WETP workshop in Cincinnati was unique among NIEHS meetings in that participants had the opportunity to witness the impact of their colleagues' research in real time. Following the keynote talks on April 30 were presentations on "Model Partnerships" and "Sharing Resources." Participants spent the afternoon in concurrent sessions and breakout sessions on specialized topics as they looked forward to the next day's Chemical Incident Scenario Exercise.

In the muted light of a massive tunnel at the Riverside Transit Center, workshop attendees witnessed the simulation of activities that would actually take place in the aftermath of a fire and explosion involving the release of large quantities of hazardous chemicals. They watched as commanders coordinated first responders from local fire departments and HAZMAT teams, who contained damage, decontaminated workers and responders, dealt with casualties, removed hazardous waste, and took other measures to ensure public health and safety.

Workshop participants witnessed firsthand the outcomes of the intensive and innovative training programs funded by WETP. They watched as leading-edge technology developed by WETP grantees made rapid mass communication possible among the many people and different communication platforms involved in the response to the incident. People who had listened to distinguished speakers call for concerted action among a broad range of organizations now experienced the real-time coordination of resources by the partnerships fostered through the efforts of WETP and ICTW staff and representatives of unions, government agencies and non-profits.

For Hughes and WETP staff members Program Analyst Kathy Ahlmark, Industrial Hygienist Sharon Beard, Education Specialist Ted Outwater and Program Analyst Jim Remington, the exercise must have evoked memories of the program's responses to such events as the World Trade Center attack and Hurricane Katrina. What was learned there transformed the ways responders will be trained to face future disasters elsewhere, as new workers join the ranks of the more than two million trained through WETP funding.

Attendees concluded their meeting and workshop in a debriefing session back at the hotel.

John Dunham of the Cincinnati Public Health Department conducts training onsite during the Chemical Incident Scenario Exercise that concluded the WETP Awardees Meeting and Workshop in Cincinnati. (Photo courtesy of Jim Remington)

Earth and material moving equipment operating at the exercise helped organizers simulate the sights and sounds of an actual disaster response in progress. (Photo courtesy of Jim Remington)

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Kleeberger Named Acting Deputy Director

By Eddy Ball

In one of his first official acts as NIEHS acting deputy director, Steve Kleeberger, Ph.D., took his place at the table during the May 21–22 meeting of the NIEHS National Advisory Environmental Health Sciences Council. He was formally introduced to the group by NIEHS Director Linda Birnbaum, Ph.D.

In a message to NIEHS employees in April, Birnbaum described Kleeberger as "a top-notch researcher of gene-environment interaction in the pathogenesis of environmental lung disease" and praised the "wealth of scientific expertise and administrative experience [he brings] to the role of acting deputy director of the NIEHS." Speaking to Council members, Birnbaum also highlighted Kleeberger's experience as an NIH grantee prior to joining the Institute in 2002.

Kleeberger is the chief of the Laboratory of Respiratory Biology and Principal Investigator of the Environmental Genetics Group. In 2006 he received the NIEHS Director's Challenge Award to lead an interdisciplinary team in translating this research to applications in human health. In 2008, he received the NIH Director's Service Award (see story).

NIEHS Acting Deputy Director Steve Kleeberger (Photo courtesy of Steve McCaw)

Prior to joining NIEHS, Kleeberger was a full professor of environmental health sciences at Johns Hopkins University Bloomberg School of Public Health. Currently, he holds adjunct professorships at the Duke University School of Medicine and University of North Carolina at Chapel Hill Schools of Medicine and Public Health. He has published more than 130 peer-reviewed articles in leading biomedical journals, as well as two dozen book chapters and invited reviews.

Kleeberger has served as a reviewer for more than 20 journals. He has also held a number of editorial board positions with such journals as *Pharmacogenetics*, *The American Journal of Respiratory* and *Critical Care Medicine*. From 2006 to 2008, Kleeberger served as deputy editor for *Environmental Health Perspectives (EHP)*, and he continues to serve on the *EHP* advisory board.

With more than 100 invited lectures in the United States, Europe, Asia and South America to his credit, Kleeberger enjoys a high profile in the scientific community. He has been president of the Inhalation Specialty Section of the Society of Toxicology, and he serves on multiple study sections at the National Institutes of Health, international advisory committees on genetic susceptibility, and Clean Air Scientific Advisory Committee (CASAC) review panels.

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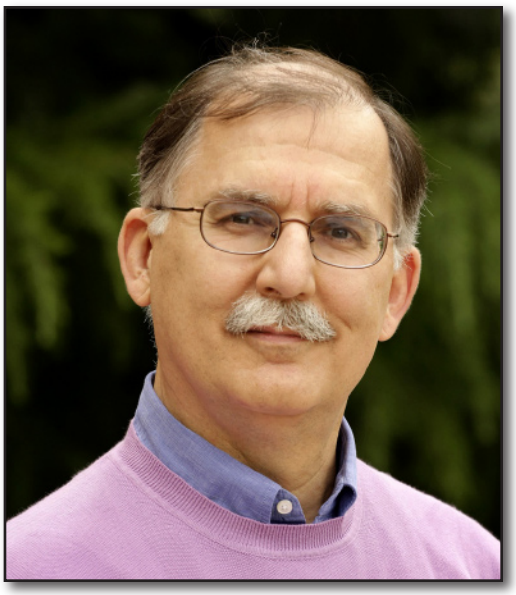
Umbach Honored by American Statistical Association

By Eddy Ball

In the world of biostatistics, there is probably no higher honor than the one to be given NIEHS Biostatistics Branch (BB) Staff Scientist David Umbach, Ph.D., by the American Statistical Association (ASA). At a ceremony during the annual ASA Joint Statistical Meeting in Washington on August 4, Umbach will become one of the elite group of ASA Fellows. The Fellows are ASA members who have been recognized for their outstanding contributions to an aspect of statistical work, leadership within the field, publications, involvement in ASA activities, and other professional activities and memberships.



Newly elected ASA Fellow David Umbach (Photo courtesy of Steve McCaw)

Umbach, who joined NIEHS in 1992, was nominated by BB Branch Chief Clarice Weinberg, Ph.D., an ASA Fellow herself since 1995. Describing her colleague's election, Weinberg said, "This is an extremely high honor — one achieved by only a tiny fraction of statisticians in their lifetime of work. Those of us who are fortunate enough to have collaborated with David have experienced firsthand his broad knowledge, wise counsel and deep insights, but it is gratifying when the recognition also comes from high places."

The focus of Umbach's work is developing new statistical tools for detecting and characterizing gene-environment interactions through epidemiologic studies, especially in regard to the design of case-control and case-parents investigations. Umbach is also a key contributor to studies of such topics as genetic susceptibility to cancer, environmental and genetic influences on neurodegenerative diseases such as Parkinson's disease and amyotrophic lateral sclerosis, effects of pesticides on respiratory diseases in the Agricultural Health Study cohort and the hormonal effects of soy formula in infants.

According to ASA rules, no more than one-third of one percent of the ASA membership may be elected each year to become new ASA Fellows. Fewer than 3,000 members have been so honored since the society began electing fellows in 1914. In addition to Umbach and Weinberg, NIEHS BB Principal Investigator Shyamal Peddada, Ph.D., who was elected in 2005, is an ASA Fellow.

ASA, which was founded in Boston in 1839, is the second oldest, continuously operating professional society in the United States. The organization serves statisticians, quantitative scientists, and users of statistics across a wealth of academic areas and applications. With an international membership of 16,000, ASA applies its expertise to many diverse tasks — from assessing environmental risk factors and assuring quality measures in industry, to examining social issues and establishing statistical standards used at all government levels.

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Children's Center Research Highlighted at Pediatric Meeting

By Eddy Ball

This year, NIEHS enjoyed a higher profile at the world's premier gathering of pediatric professionals — the Pediatric Academic Societies (PAS) Annual Meeting May 2–5 in Baltimore. The meeting featured three special sessions on NIEHS Children's Environmental Health Center research developed by NIEHS Health Scientist Administrator Kimberly Gray, Ph.D. NIEHS grantees were also participants and presenters in four other sessions at the meeting.

Gray, above, is shown in her element — interacting with grantees at a 2008 meeting of cardiopulmonary researchers, several of them involved specifically in children's environmental health. (Photo courtesy of Steve McCaw)

Gray said one of her goals at the meeting was to help integrate the Children's Environmental Health program into the spectrum of other NIEHS-funded research in important critical areas of development, including the role of DNA methylation and the characterization of developmental health effects, such as autism and ADHD, related to environmental exposures.

The NIEHS presence at the PAS Annual Meeting involved special sessions with grantees and principal investigators from each of the ten institutions in the NIEHS Centers for Children's Environmental Health and Disease Prevention Research program.

- A Hot Topic symposium on **"Epigenomic Changes Related to Environmental Exposures in Children"** May 2, providing an integrated summary of new studies of the relationship between the environment and epigenetics in children conducted by investigators from the Children's Environmental Health Centers, was chaired by Frederica Perera, Dr.P.H., Mailman School of Public Health at Columbia University, and Robert Wright, M.D., School of Public Health at Harvard University.

- A Mini-Course on **"Contributing Factors That Influence the Relationship between Environmental Exposures and Children's Health,"** May 3, exploring the effects of other factors that influence the biological response to environment agents and the risk of adverse health outcomes in children based on

research by NIEHS and U.S. EPA Children's Environmental Health and Disease Prevention Research Center investigators, was chaired by Gray. Participants included investigators from Harvard University, the University of Southern California, University of California Berkeley and Columbia University, as well as a new NIEHS early stage investigator from Duke University, Catherine Hoyo, Ph.D.

- A Topic Symposium on **"Environmental Influences on Development Disorders and Dysfunction in Young Children,"** May 4, focusing on the role of the environment in the etiology or exacerabation in mental health disease and disorders in children as well as the potential causal pathways and the importance of new measures of intermediate clinical phenotypes and the effects of drug therapies as potential confounders, was chaired by Gray and Virginia Rauh, Sc.D., Columbia University Mailman School of Public Health.

NIEHS grantees also participated in a Platform Session on "Environmental Health," a Special Symposium on "The National Children's Study: Moving into the Field," and the second Annual Debate on Controversies in Pediatric Environmental Health, "Should Pediatricians Advise Parents to feed their Children Organic Foods?" On the final day of the meeting, a topic symposium on "Environmental Contributions to Autism Risk" featured NIEHS-funded researchers from the University of California, Davis Medical Investigation of Neurodevelopmental Disorders (M.I.N.D.) Institute.

The PAS is comprised of four individual pediatric organizations that co-sponsor the PAS Annual Meeting— the American Pediatric Society, the Society for Pediatric Research, the Academic Pediatric Association and the American Academy of Pediatrics. The PAS also collaborate with 22 Alliance Partners, which are subspecialty societies and clubs that meet or co-host programming during the PAS Annual Meeting.

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Hrynkow Represents NIEHS at AAAS Forum

By Eddy Ball

Continuing her work in forging partnerships and cross-disciplinary collaborations in global environmental health, NIEHS Associate Director Sharon Hrynkow, Ph.D., organized and chaired a panel discussion on the linked issues of climate, energy and health at the 2009 AAAS Forum on Science Technology and Policy. Featuring experts in global health and Obama administration policy leaders, the meeting was held April 30–May 1 at the Ronald Reagan Building and International Trade Center in Washington.

NIEHS Associate Director Sharon Hrynkow (Photo courtesy of AAAS)

The 34th annual forum brought together over 600 scientists, policy makers and students, plus more than two dozen journalists, for two days of discussions and lectures on the nexus of science and public policy. One goal of the meeting was to shine light on key science issues under debate in the global policy arena as the U.S. prepares for the UN Climate Change Conference in Copenhagen this December. Hrynkow, who also serves as chair of the AAAS Committee on Science, Engineering and Public Policy, said she was pleased to have an opportunity to lead a discussion on what she called the "linked agenda" of climate change, energy strategies and health issues, and the related policy implications.

"Addressing climate change requires concurrent thinking across multiple scientific disciplines," Hrynkow commented in her opening remarks. "Health and climate, both directly and indirectly, are intricately linked."

At mid-session, the panel included, left to right, Smith, Detchon, Corvalán and Greenbaum. Dobson, who was delayed, offered his perspective as the final speaker of the session. (Photo courtesy of AAAS)

Speakers in Hrynkow's session explored the direct and indirect effects of the changing climate on human health and adaptive strategies for minimizing the consequences. Panelists included Kirk R. Smith, Ph.D., of the University of California, Berkeley, Carlos Corvalán, Ph.D., of the Pan American Health Organization (PAHO), Daniel Greenbaum, of the Health Effects Institute, Reid Detchon of the UN Foundation and Energy Future Coalition, and Andrew Dobson, Ph.D., of Princeton University.

Smith, who was the first speaker at the session, focused on the co-benefits of reducing harmful gases and pollutants, encouraging more equitable levels of red meat consumption and promoting reproductive health as part of a broader strategy to tackle climate change. He was followed by Corvalán, who underscored the disproportionate impact of climate-change sensitive diseases on children and described the World Health Organization and PAHO commitments to tackling climate change through strengthening health systems, supporting local research and building capacity for health professionals.

Pointing to mounting evidence linking ozone to respiratory illness and premature mortality, Greenbaum warned that climate change would lead to warmer temperatures that favor the creation of ozone. In his remarks, Detchon called for expanded use of electric cars and cleaner alternatives to oil that do not require the addition of aromatics to boost octane. Closing out the session, Dobson described the anticipated effects of climate change on infectious disease transmission patterns and lamented the shortage of experts on the effects of climate change on human health.

The keynote talk at the forum was presented by John Holdren, Ph.D., former president of AAAS, who now serves as assistant to the President for science and technology and director of the Office of Science and Technology Policy. Holdren underscored President Obama's commitment to science and assured his listeners that "science and technology is clearly back in the United States." Holdren also told the audience, "The voices of the climate science community are being heard." Other major speakers were MIT President Susan Hockfield, Ph.D., and Secretary of Energy Steven Chu, Ph.D., each of whom underscored the importance of multi-disciplinary scientific approaches in order to protect human health and the environment.

The AAAS Forum on Science and Technology Policy is regarded as the premier event of its kind in the United States, focusing on federal budget and research and development issues, public- and private-sector research, education, innovation, and other high-profile domestic and international science and technology issues.

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NIEHS Supporting Greenhouse Gas Emissions Study Group

By Eddy Ball

NIEHS Associate Director Chris Portier, Ph.D., has the lead role for NIEHS on an international team of scientists investigating the potential health benefits of reducing greenhouse gas emissions to help combat climate change. The results of the study will inform the UN Climate Change Conference in Copenhagen in December.

The study will be led by Sir Andrew Haines, M.D., the director and a professor at the London School of Hygiene and Tropical Medicine (LSHTM). Portier is head of the NIEHS Office of Risk Assessment Research and part of a leadership team with assignments in the areas of global environmental health and climate change.

Much of the climate change debate has focused on environmental impacts, but climate change is also likely to affect the health of millions of people. Threats include heat waves and flooding, changing patterns of infectious diseases such as malaria and dengue, and the risk that hundreds of thousands of people will be displaced by water scarcity and rising sea levels. The effects are expected to be greatest in developing countries.

However, mitigation strategies — policies aimed at reducing greenhouse gas emissions to tackle climate change — could also have positive implications for health. For example, encouraging people to walk rather than take the car could make populations more physically active, reducing obesity while also cutting urban pollution and road traffic accidents. Similarly, moving to greener fuels could reduce outdoor air pollution and improve public health.

The international team of scientists will model the impacts of policies aimed at reducing greenhouse gas emissions in both developed and developing countries. The researchers will focus on four key sectors — energy, transport, the built environment, and food and agriculture.

The expert group will explore more detailed case studies. These will include examples relating to domestic energy-saving measures in the United Kingdom (U.K.), household fuel use in India, power generation, urban transport changes and initiatives to reduce the use of cars, and the impact of changing agricultural practices and reducing meat consumption to reduce livestock emissions

The £405,000 study is being funded by the Wellcome Trust, the Royal College of Physicians, Economic and Social Research Council, U.K. Department of Health, U.K. National Institute for Health Research, NIEHS and U.K. Academy of Medical Sciences.

Along with his work on the environmental issues and their impacts on human health, NIEHS researcher Chris Portier works closely with the WHO and other international bodies on risks to human health. (Photo courtesy of Steve McCaw)

Haines is a member of the WHO Advisory Committee on Health Research and has worked internationally in Nepal, Jamaica, Canada and the U.S. (Photo courtesy of the London School of Hygiene and Tropical Medicine)

"Reducing greenhouse gas emissions is essential if we are to help tackle climate change, but we need to better understand the potential health impact of these strategies," says Sir Mark Walport, Ph.D., director of the Wellcome Trust. "Climate change could have a devastating impact on people's health, with those in the developing world at greatest risk. Well-planned and successfully-implemented climate change mitigation strategies could actually improve public health — a win-win solution."

This study is intended to inform negotiations at the UN Climate Change Conference in Copenhagen, as political leaders meet to reach agreements on targets post-Kyoto. The Wellcome Trust and the LSHTM will be working with the World Health Organization (WHO) to raise awareness of this research and the health impacts of climate change during the course of the year.

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As director of the Wellcome Trust, Walport oversees more than £600 million in charitable spending every year, both in the U.K. and internationally, achieving the organization's mission — supporting and promoting research to improve the health of humans and animals. (Photo courtesy of the Wellcome Trust)

Clinical Research Unit Ribbon Cutting July 27

By Eddy Ball

NIEHS will cut the ribbon on its new Clinical Research Unit (CRU) before an audience of scientists and distinguished visitors on July 27 at its Research Triangle Park, NC campus. NIEHS and National Toxicology Program Director Linda Birnbaum, Ph.D., and Acting Clinical Director Darryl Zeldin, M.D., the event host and moderator, are slated to speak at the ceremony, which will also feature other speakers and an afternoon of scientific seminars. Distinguished guests include Representative David Price, Ph.D., US Senator Kay Hagan and NIH Deputy Director for Intramural Research Michael Gottesman, M.D.

When Birnbaum approved opening the CRU earlier this year, she described it as "an important resource for scientific collaboration across our entire Institute and with local researchers. Our ultimate goal for the CRU," she said, "is to enable researchers to translate their basic laboratory findings to humans and to enhance the public health relevance of our research." During the weeks leading up to the ribbon cutting, the CRU will collect its first samples from study participants.

According to Birnbaum, the kinds of activities to be supported by the CRU include simple medical tests and procedures such as collection of easily accessible body fluids and tissues, pulmonary function

The CRU building is nestled in the trees next to the main NIEHS building in Research Triangle Park, NC. (Photo courtesy of Steve McCaw)

studies, allergy skin testing and ultrasound. “All studies will undergo rigorous scientific review,” she said, “and will require approval by a CRU Utilization Committee, the Institutional Review Board and the Acting Clinical Director. This procedure will assure that the guidelines are followed and that all studies are safe.”

The CRU recently hosted colleagues from the NIH Clinical Center (NIH CC) for a site visit, which included touring the unit, reviewing standard operating procedures and making recommendations to enhance efficiency and quality of care. The group included Deputy Director for Clinical Care David Henderson, M.D., Special Assistant to the Deputy Director for Clinical Care Laura Lee, R.N., Hospital Safety Officer Michele Evans, Dr. P.H., Chief Information Officer Jon McKeeby, D.Sc., and Clinical Nurse Informaticist Norma Street, R.N.

The facility is set up for seeing patients and running non-invasive functional tests as part of clinical research at NIEHS. (Photo courtesy of Steve McCaw)

NIEHS interest in asthma and other respiratory disease is reflected by the equipment in the CRU pulmonary function lab. (Photo courtesy of Steve McCaw)

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NIEHS Participates in New One Health Initiative

By Eddy Ball

Long before news about the H1N1 “swine flu” virus concerned people around the world, leaders in the animal health community were already organizing to better understand and deal with the growing health threat posed by multi-host pathogens. On May 1, two NIEHS leaders — Associate Director Allen Dearry, Ph.D., and Rear Admiral Bill Stokes, D.V.M., director of National Toxicology Program (NTP) inter-agency programs on alternative methods — joined colleagues from area universities and organizations at a One Health Roundtable at the Hamner Institutes for Health Sciences in Research Triangle Park (RTP).

One Health is an initiative conceived in 2006 by then American Veterinary Medical Association (AVMA) President Roger Mahr, D.V.M., to lead a collaborative effort involving multiple disciplines working locally, nationally and globally. An example of cases where One Health collaborations have been especially effective is in combating zoonotic diseases — ones transferred from animals to humans, such as H1N1, avian influenza and West Nile virus. These pathogens cause approximately 60 percent of all recognized human disease and 70 percent or more of newly emerging infectious diseases.

According to One Health leaders, climate change and a growing demand for food from animal sources are exacerbating the impact of the environment on the health of people and animals. Potential increases in emerging and re-emerging zoonotic infections could challenge the capacity of existing comparative health expertise and public health resources.

Stokes, a career officer in the U.S. Public Health Service Commissioned Corps, is a distinguished member of the AVMA and a member of the One Health Joint Steering Committee. He also served on the AVMA's One Health Initiative Task Force that published its report on the new program last year. Dearry, who focuses on environmental public health, is part of the Institute's leadership team assigned to the field of global environmental health.

NIEHS Associate Director Allen Dearry (Photo courtesy of Steve McCaw)

Along with Dearry and Stokes, participants at the RTP roundtable included representatives of the Hamner Institutes, North Carolina State University College of Veterinary Medicine, University of North Carolina Gillings School of Public Health, Duke University School of Medicine, and North Carolina Department of Health and Human Services.

Participants shared information about their expertise in areas relevant to the human health implications of emerging multi-host pathogens and identified training and infrastructure needs. Stokes and Dearry described the work of NIEHS researchers in the areas of water- and vector-borne disease and harmful algal blooms, as well as NIEHS involvement in research on cancer, obesity, neurodegenerative diseases and the environment. They explained that NIEHS supports One Health as a part of the Institute's focus on disease prevention.

The One Health Roundtable in RTP was one of several organizational meetings convened nationwide to involve governmental, educational and research organizations in a concerted effort for accomplishing four major goals:

- Develop, implement and sustain an integrated national strategy for improved public health based on the principles of One Health
- Create national and international awareness within the health science professions, the broad scientific community, government institutions, the political leadership and the general public of the power of One Health to improve the health of people, animals and the environment
- Illustrate the value of implementing One Health through specific demonstration models and projects
- Extend One Health to the international community to achieve tangible improvements in health worldwide

The One Health Vision

Vision Statement
To promote and improve the health of humans, animals and our environment, individually and col-lectively, by encouraging and ensuring the acceptance and adoption of One Health and its associated activities.

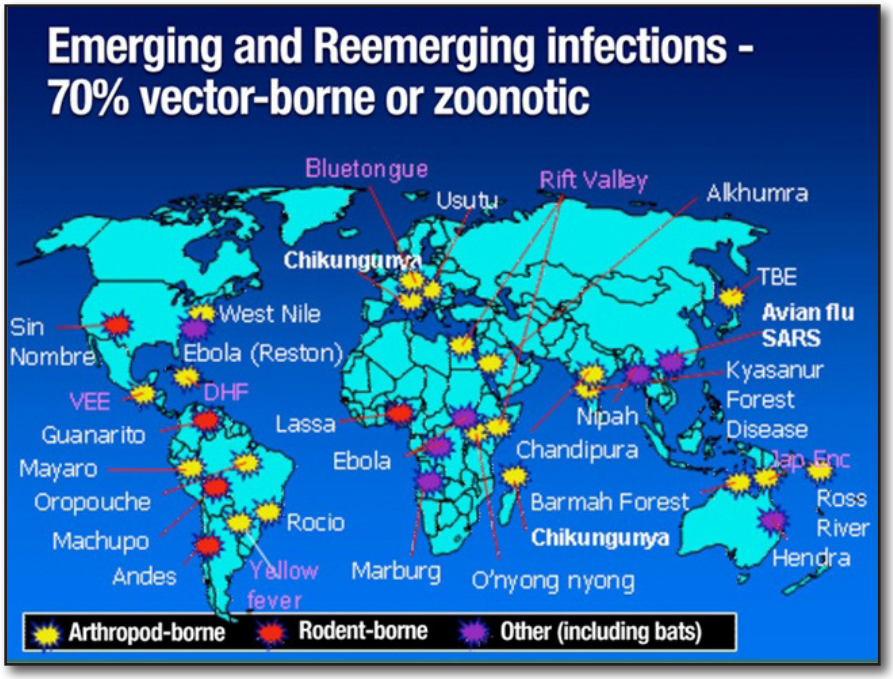
Definition of "One Health"
One Health is the collaborative effort of multiple disciplines-working locally, nationally, and globally to attain optimal health for people, animals and our environment.

The Scope of "One Health"
The scope of One Health is impressive, broad, and growing.

One Health gained an important ally early in the planning process when the American Medical Association (AMA) partnered with the AVMA on the One Health concept. The One Health Joint Steering Committee now has nearly twenty participating member organizations, including the NIEHS and NTP, U.S. Department of Agriculture, Centers for Disease Control and Prevention, National Park Service, Association of American Veterinary Medical Colleges and Association of American Medical Colleges. One Health received a $100,000 program implementation grant from the Rockefeller Foundation earlier this year.

Stokes serves as director of the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) and executive director of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM). (Photo courtesy of Steve McCaw)

Left to right, Stokes gathers with One Health leaders Mahr, Darol Dodd, Ph.D., director of the Division of Toxicology and Preclinical Studies at The Hamner Institutes for Health Sciences, and AMA representative Albert Osbahr, M.D. (Photo courtesy of William Stokes)



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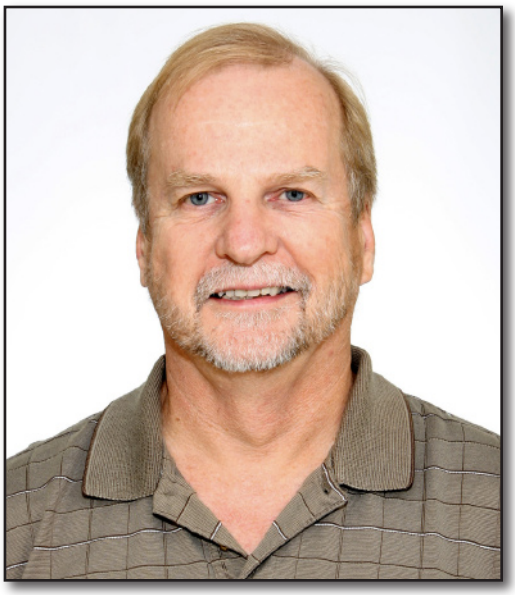
EPA Leader Reports on Progress in Toxicity Testing

By Eddy Ball

Robert Kavlock, Ph.D., visited NIEHS on May 7 to present a status report on the ToxCast™ program he oversees as the director of the National Center for Computational Toxicology (NCCT) at the U.S. Environmental Protection Agency (EPA). EPA is a partner in the five-year Memorandum of Understanding (MOU) signed in 2008 with NIEHS and the National Human Genome Research Institute to improve the evaluation of health risks posed by chemicals found in the environment.



Kavlock told the audience, "Toxicology is poised to change its stripes." Looking ahead, he referred to the ToxCast Data Analysis Summit May 14–15 at the EPA regional headquarters in Research Triangle Park. (Photo courtesy of Robert Kavlock)

Members of this MOU are informally known as the Tox21 community — for toxicology in the 21st century. This seminar was sponsored by the National Toxicology Program (NTP) Biomolecular Screening Branch, which is responsible for managing the NTP's High Throughput Screening (HTS) Initiative. The presentation by Kavlock, "ToxCast: Profiling Bioactivity, Identifying Pathways and Predicting Toxicity," attracted a group of scientists from NIEHS and the NTP, including Linda Birnbaum, Ph.D., director of both organizations.

The goal of ToxCast™ is to develop a high throughput-based program for evaluating the biological targets of environmental chemicals responsible for adverse effects in exposed individuals. EPA needs such a process in order to close the large information gap that exists for thousands of man-made chemicals present in the environment. EPA began planning the ToxCast™ program in fiscal year (FY) 2005, with a "reduce-to-practice" target date of FY 2012.

As he talked about ToxCast™, Kavlock reviewed progress by the NCCT and the other Tox21 partners toward implementing the vision outlined in a 2007 report by the National Research Council on a vision and strategy for toxicity testing in the 21st century. Kavlock also said he was encouraged by the growing cooperation that NCCT is enjoying from manufacturers and drug companies — potentially valuable sources of privileged toxicity data.

Raymond Tice, Ph.D., was the host of the presentation. Tice is deputy director of the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), acting chief of the NTP Biomolecular Screening Branch and HTS Initiative coordinator. (Photo courtesy of Steve McCaw)

According to Kavlock, the toxicology community now acknowledges that by itself the classical model for animal studies is inadequate for the task of assessing the toxicity of the growing number of chemicals in the environment. Animal studies are expensive — costing millions of dollars for a single chemical — time consuming and controversial, he explained. The challenge scientists and regulators face involves developing cost-effective HTS assays to assess biochemical pathways triggered by chemicals, their "biological fingerprints" and "toxicity signatures," that can be used in predicting the potential health effects of exposures.

"We don't rely on a single technology," Kavlock noted as he reviewed the range of assays the program is using. As an example, he pointed to five different methods the program uses for checking whether a chemical can act as an estrogen.

ToxCast™ examines how each chemical affects a variety of biological processes and compiles the information into a huge database to complement existing animal data. This data will be combined with information on the chemical's structure and behavior in the human body to help quickly classify chemicals based on their potential for human or environmental harm. Phase One of ToxCast™ has produced data from 320 chemicals, approximately 500 *in vitro* assays and some 100 *in vivo* endpoints, Kavlock said. The data analysis challenge for such a massive amount of data is daunting. "It's like the early days of microarrays," he added. "We have lots of data, and we're looking for the best ways to interpret the observations."

Phase Two of the program, set to start later this year, will include a groundbreaking collaboration with Pfizer, Inc. To help validate the approach for predicting human toxicity, Pfizer has agreed to provide EPA with information on drugs that were found to cause toxicity in clinical trials.

While he and his audience were upbeat about the future of ToxCast™ and alternative toxicity testing, Kavlock acknowledged the challenges ahead. "The deluge is coming," he said. "We are really on the tip of the iceberg in terms of looking at the data."

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Tinkle Represents NIEHS and NIH at Drug Conference

By Eddy Ball

NIEHS Senior Science Advisor Sally Tinkle, Ph.D., spoke at the Fourth Annual Chapel Hill Drug Conference May 13–14 at the University of North Carolina at Chapel Hill. She was the sole NIH representative at the meeting of academic and private sector experts considering "The Use of Nanotechnology to Create Safe and Effective Therapeutic and Diagnostic Products."

Tinkle is the lead representative for NIEHS on trans-NIH, interagency and international nanotechnology and NanoHealth working groups. On May 14, she spoke on "Exploring the Interface Between Nanomedicine and Nanobiology: The NIH/NIEHS Perspective."

As in earlier talks, Tinkle urged her audience to evaluate carefully the impact of nanotechnology and nanomaterials throughout their life cycles, from manufacture through use and disposal, to understand their potential long-term impact on human health. She opened her talk by emphasizing that "NIH is the steward of medical and behavioral research for the U.S." with a responsibility for supporting the pursuit of "knowledge to prevent, detect, diagnose and treat disease and disability."

NIEHS Senior Science Advisor Sally Tinkle receives a plaque of appreciation from from session chair Rudy Juliano, Ph.D. Juliano is Boshamer Distinguished Professor at UNC-CH, a principal investigator at the Carolina Center of Cancer Nanotechnology Excellence and co-director of the Institute for Nanomedicine (Photo courtesy of Sally Tinkle)

Tinkle reviewed the concepts of a comprehensive basic and clinical research agenda to understand the impact of exposures along human biochemical pathways and the direction of NIH and NIEHS programs in the areas of naonomaterials and nanotechnology. She pointed to the value of partnerships in such endeavors as the development of enabling technologies, including high-throughput screening in toxicology testing and chemical databases, that will help researchers better understand potentially harmful exposures and how to limit and treat their health effects.

Tinkle appealed to shared interests that bridge disciplines and sectors as they strive to realize the enormous potential of nanotechnology in the areas of medicine, engineering and consumer products. She called for cooperation and partnerships in the effort to integrate human health and ecotoxicology.

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Science Notebook

Nobel Laureate Examines Immune Cell Deviations

By Robin Arnette

Lymphoma is a term used to describe a group of cancers that affect lymphocytes — the cells involved in the immune system. Pathologists who view these cancerous lymphocytes under a microscope usually see one type of cell, but sometimes two different cell types exist in the same sample. Nobel Laureate Andrew Fire, Ph.D., studies the diversity of these cells and the normal cellular rearrangements that occur in the immune system. His NIEHS Distinguished Lecture on "Cellular Responses to Foreign Nucleic Acids" took place on May 19, and Farhad Imani, Ph.D., a fellow immunologist and principal investigator in the Laboratory of Respiratory Biology, hosted the seminar.

Fire is a professor of Pathology and Genetics at the Stanford University School of Medicine and a member of the National Academy of Sciences and the American Academy of Arts and Sciences. He shared the 2006 Nobel Prize in Physiology or Medicine with Craig Mello, Ph.D., for the discovery of RNA interference (RNAi) — gene silencing by double-stranded RNA. (Photo courtesy of Linda A. Cicero of the Stanford News Service)

Fire said that his recent research focus came as a suggestion from a member of his lab, Scott Boyd, M.D. Boyd was looking at lymphoma samples and found one that had both large and small cells. "He wanted to know if the two groups of abnormal cells had a common origin or if they were two separate malignancies that were present in the same individual," Fire added. "He thought that he might be able to address the question by looking at the population of DNA rearrangement present in this individual."

To study the many rearrangements that occur in tumors, Fire said that it was necessary to understand the normal rearrangements that occur in the immune system. He explained that a natural progenitor blood cell that will eventually become an antibody-producing cell population doesn't start out with that capability. It has to combine one of the V, D, J and constant regions to make a functional coding region that can encode an immunoglobin that recognizes something.

The system adds a few nucleotides in the junction spaces to give it more diversity. "Once that happens the cell starts making antibodies and they move to the surface of the cell," Fire continued. "If an organism's immune system recognizes something as 'self,' it gets rid of that cell, but if the system recognizes something as foreign, it keeps that cell and mounts an immune response."

This recognition triggers cycles of hypermutation and proliferation, but the process has the potential to go awry. Fire explained that a population of cells could "think" that it's recognizing a foreign antigen and starts proliferating when it is really recognizing a self antigen. This scenario occurs in many autoimmune diseases.

Fire took blood samples from patients and extracted DNA from the mononuclear lymphocytes in the blood. Using standard primers that covered the VDJ recombination junction, he employed PCR to generate many copies of the particular sequence. He then utilized high-throughput sequencing technology by attaching little

beads that bind one molecule of DNA from one of the recombined cells. By barcoding the samples with small pieces of nucleotides on both sides of the PCR-generated sequences, Fire incorporated 75–100 samples on a single sequencing run.

Fire wrote some of the software that displayed the sequences as images. Each sample was a square panel that had approximately 1000 sequences, which were represented as spots of V and J combinations. Each V and J combination spot had a color and size that corresponded to the number of different instances that particular combination was seen in the sequence set. Normal people have a lot of VJ combinations, while those with lymphomas have a very strong signal in one spot. Each lymphoma has its own individual spot pattern. When Fire looked at the image from the original sample that Boyd examined, he saw that it contained two large spots, which meant that the patient had two immunoglobulin rearrangements. The findings suggest that the lymphoma arose from two distinct cells.

The technique developed by Fire's lab is applicable to other diseases with deviations in the immunome — and these results are just the beginning. "We are interested in understanding people's immune systems, in cases of different histories of both disease and environmental exposure."

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Birnbaum is Plenary Lecturer at BFR2009

By Eddy Ball

NIEHS and National Toxicology Program (NTP) Director Linda Birnbaum, Ph.D., was back on very familiar turf when she delivered a plenary lecture at the 11th Annual Workshop on Brominated Flame Retardants (BFR2009) held May 19–20 at the Government Conference Centre in Ottawa. Her talk on "Effects of Brominated Flame Retardants: Health and Regulations" set the stage for the second day of presentations, discussions and poster displays at the workshop.

Jointly sponsored by Health Canada and Environment Canada, the workshop focused on highlighting innovative research on various aspects of novel and legacy brominated fire retardants (BFRs), including analytical chemistry, toxicology, fate and environmental behavior, monitoring and surveillance, and risk assessment and management. Birnbaum, recognized as a world expert on the toxicology of BFRs, offered an overview of the various compounds that are present in consumer products found in virtually every home and workplace in North America along with a review of research into their potential health effects.

As Birnbaum explained, despite banning or suspending manufacture of the Deca form of polybrominated diphenyl ethers (PBDEs) in recent years, Deca and other PBDEs are ubiquitous in the environment, leading to concerns about continued exposures for people and wildlife that have been linked to endocrine disruption and developmental neurotoxicity. Some environmentalists and scientists, she noted, also question the "safer" alternative BFRs developed to replace them. These chemicals remain unregulated in most places.

Many of the BFRs are bioaccumulative and persistent and can act as endocrine disruptors in animals. BFRs are widely dispersed and have been found in animals living in environments where the compounds are not commonly used, such as the Arctic. Research with animals points to their potential toxicity or mutagenicity

in animal studies and their disruption of the estrogen, androgen and thyroid hormone systems, but only one of the compounds, Deca, has been tested in two-year rodent studies. In those studies, Deca was shown to be carcinogenic.

Birnbaum chose to delay opening her own lab at NIEHS, but she remains passionate about her research into the health effects of BFRs. (Photo courtesy of Steve McCaw)

Birnbaum reviewed experimental animals studies and epidemiological studies that have raised concerns about other health effects of PBDE mixtures and cogeners, including hepatotoxicity and the induction of xenobiotic metabolizing enzymes. Few human studies have been performed on newer BFRs, such as tetrabromobisphenol A (TBBPA) and hexabromocyclododecane (HBCD), although animal studies and *in vitro* data suggest similar health effects to those found in PBDE studies. Even less is known about the additive effects of PBDEs and other chemicals.

Birnbaum's talk was followed by three focused sessions that elaborated on the themes of her presentation.

- "Effects of BFRs in Wildlife," chaired by Pamela Martin of Environment Canada
- "Effects of BFRs in Humans and Laboratory Studies," chaired by Thea Rawn, Ph.D., of Health Canada
- "Assessment of BFRs," chaired by Mark Feeley of Health Canada

The workshop concluded with a look forward to BFR2010 — the fifth international symposium on BFRs, in Kyoto, Japan. Birnbaum is one of two U.S. representatives on the meeting's International Scientific Committee.

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Guest Lecturer Offers New Insight into Heritable Epigenetic Changes

By Negin Martin

Christophe Herman, Ph.D., a professor in the Department of Molecular and Human Genetics at Baylor College of Medicine, gave the latest talk in the NIEHS Laboratory of Molecular Genetics (LMG) Fellows Invited Lecture Series on May 18. His presentation, titled "Beyond Mutation: Transcription and Protein Folding Errors Generate Heritable Epigenetic Change," was hosted by NIEHS Spontaneous Mutation and Repair Group Visiting Fellow Libertad Garcia Villada, Ph.D.

Until recently, mutations in DNA sequences were considered to be the only form of heritable changes that defined phenotype. However, many cells with similar genes have different phenotypes. Epigenetic — "epi" meaning "over" or "above" in Greek — research such as Herman's bridges this gap in understanding heredity by investigating factors other than DNA mutations that effect phenotype.

Epigenetics is the study of heritable changes that alter gene expression without any changes to DNA sequence. DNA methylation, histone acetylation and small interfering RNAs are examples of heritable epigenetic gene regulation. Unlike DNA mutations, epigenetic changes are often reversible.

Herman has studied a number of other physiological systems, including heat shock proteins, metalloproteases and transcriptional regulators, that can be involved in epigenetic alteration. His lecture at NIEHS was divided into two sections, illustrating examples of heritable gene regulation by bistable switches and their dysregulation by protein misfolding or transcription errors.

As Herman explained, genes do not manifest any phenotypes unless they are expressed. Bistable switches often regulate cell differentiation by turning genes on or off. To qualify as a switch, a protein needs to be poorly expressed and to be involved in a positive or double negative feed back loop. Abundant proteins are difficult to silence or modify.

Herman's group used the well-studied *lac* operon system in *Escherichia coli* bacteria to study epigenetic modifications by a poorly transcribed repressor. The *lac* repressor is transcribed once per cell generation, and its depletion turns the *lacZYA* gene on. The *lacY* gene product increases permeability to an inducer that keeps the gene on. In short, if the gene is on it resists being turned off by transporting its own inducer. By replacing the *lacA* gene with green fluorescent protein (GFP) in this bistable model, his team was able to monitor transient errors in transcription and determine their hereditability.

According to Herman, when RNA transcription is error prone due to polymerase infidelity or absence of quality control proteins such as GreA and GreB, epigenetic switching becomes more prevalent. Hence, using bacteria as a model organism, Herman showed that such errors in transcription are heritable.

Protein translation and misfolding also contribute to epigenetic changes. Herman pointed to immunity control of lambda as an example of an epigenetic switch by a protein that is poorly translated.

Herman used a slide of the 1929 painting "The Treachery of Images (This is not a pipe)" by the Belgian surrealist René Magritte to open his talk, underscoring that what appears to be the result of a DNA mutation may in fact not be one at all — just as Magritte's painting is not a pipe but an image of one. (Photo courtesy of Steve McCaw)

NIEHS Drosophila Chromosome Structure Group Principal Investigator James Mason, Ph.D., was among the scientists drawn to Herman's presentation on heritable gene regulation by bistable switches and their dysregulation by protein misfolding or transcription errors. (Photo courtesy of Steve McCaw)

Throughout his talk, Herman called on analogies to clarify complicated concepts. In order to explain the importance of background in determining function, Herman used the physical state of agar. If agar is moved from a refrigerated environment where it is solid to a warmer temperature at 55° C, it retains its solid form. In contrast, if agar is boiled, it becomes liquid and remains liquid at 55° C. Therefore, the same substance exposed to two different backgrounds could illicit different physical properties at identical temperatures. This excellent analogy helped to explain the basic principle of epigenetics – that environmental background can dictate phenotype without altering DNA sequence.

As Herman's talk demonstrated, epigenetic mechanisms of inheritance are especially important in understanding cell response to the environment and toxins. Manipulating gene expression, rather than genetic sequence, may offer novel ways for reprogramming cell function and curing or preventing disease.

(Negin Martin, Ph.D., is a biologist in the NIEHS Laboratory of Neurobiology Viral Vector Core Facility and a 2009 Science Communication Fellow with Environmental Health Sciences. She recently completed a postdoctoral fellowship with the NIEHS Membrane Signaling Group.)

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Garcia Villada, left, monitored the question and answer session that followed Herman's lecture. (Photo courtesy of Steve McCaw)

Seminar Highlights a Promising HIV Inhibitor

By Robin Arnette

Structural biologists use techniques such as X-ray crystallography, mass spectrometry and nuclear magnetic resonance (NMR) to determine the structure and function of molecules. One such specialist visited NIEHS on May 7 to talk about her work on cyanovirin-N (CV-N), an unusual protein that inhibits the human immunodeficiency virus-1 (HIV-1) — the causative agent of AIDS. Angela M. Gronenborn, Ph.D., presented "The CVNH Family of Lectins: Structure, Folding and Sugar Binding" as part of the NIEHS Laboratory of Structural Biology (LSB) Seminar Series. Kelly Mercier, Ph.D., a fellow in the LSB Nuclear Magnetic Resonance (NMR) Group hosted the lecture.

Gronenborn, who was elected to the prestigious National Academy of Sciences in 2007, is the Rosalind Franklin professor and chair of the Department of Structural Biology at the University of Pittsburgh Medical Center (UPMC). (Photo courtesy of Angela Gronenborn and UPMC)

Over the course of her career, Gronenborn has studied a large number of proteins, but she chose to focus on one serendipitous molecule for her talk. "Mike Boyd at NCI was screening extract from the cyanobacterium *Nostoc ellipsosporum* for anti-HIV activity and found something interesting, a protein now called cyanovirin-N (CV-N)," she said. "I attended an NMR meeting [afterwards], and a colleague asked me to look at the spectrum of this protein. At the time, I didn't know what it was, but I was determined to find out."

Other scientists had concluded that CV-N was stable under stringent conditions. During the purification process, the researchers treated it with alcohol and 0.1 percent sodium dodecyl sulfate (SDS) and boiled it, but it still had activity. The team eventually ascertained that it was 11 kDa with two disulfide bonds, but the most fascinating finding was that it wasn't related to any sequences in the protein sequence database.

Gronenborn furthered the work by using NMR to determine that the protein was a monomer in solution, made up mostly of β-sheets in a completely new fold — no similar structure had been deposited in the Protein Structure Database (PSdb). Surprisingly, X-ray crystallography showed a domain-swapped dimer in the crystal state. Gronenborn explained that domain swapping produces an intertwined dimer when a domain of monomer A is exchanged with an identical domain of monomer B. To her amazement, additional experiments revealed that CV-N was also able to adopt three different confirmations depending on the environment. "When you pull up the coordinates of a protein from the PSdb," Gronenborn warned, "just know that the structure you see exists under the conditions at which the data were collected; there may be alternative confirmations."

Because of its anti-viral activity, CV-N is an important player in the fight against AIDS. Virologists had discovered that HIV has a protein on its surface called envelope glycoprotein (gp120) that is highly glycosylated, which means it contains many sugar molecules. If researchers add CV-N to a mix of human cells and HIV, the CV-N binds to the sugars on the gp120 and prevents the virus from infecting the cells. Gronenborn used NMR to map the binding site of the sugar on CV-N and also found that the 3' and 4' hydroxyl groups on terminal mannose units on the sugar are crucial for the interaction.

The research team spent several years doing this work, and during that time, sequences of CV-N homologues from other organisms were deposited into the gene bank, including ferns and two species of fungi — the Tuscany White Truffle (*Tuber borchii*) and the red bread mold (*Neurospora crassa*). Gronenborn examined the structure of these related versions of CV-N and found that they have slight variations in structure, but a similar architecture overall.

Gronenborn concluded her seminar by saying another scientist discovered that the *N. crassa* CV-N was related to a *Clock* gene, which is responsible for the 24-hour cycle of circadian rhythms in living organisms. She said, "At least in *N. crassa*, we know the protein has something to do with the biorhythms of an organism, but in the others we haven't a clue."

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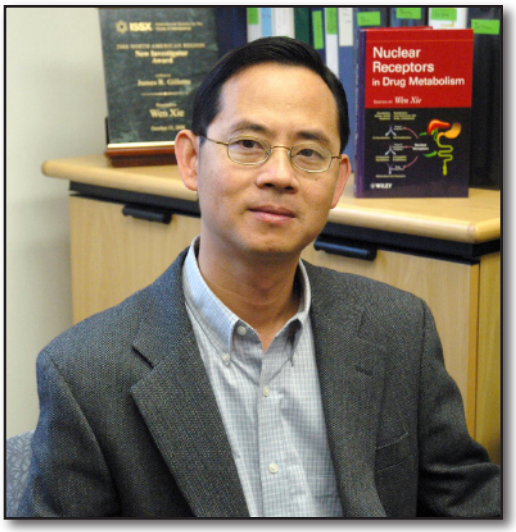
Xie Explores Hormone Regulation by Nuclear Receptors

By Laura Hall

On April 30, Wen Xie, M.D., Ph.D., presented a seminar at NIEHS on "Nuclear Receptor-Mediated Gene Regulation in Hormonal Homeostasis" as part of the NIEHS Laboratory of Pharmacology (LP) and Laboratory of Molecular Toxicology Seminar Series. His talk was hosted by NIEHS Principal Investigator Joyce Goldstein, Ph.D., head of the LP Human Metabolism Group. Xie discussed a newly established role of liver X receptor (LXR) in hormonal homeostasis in mice that may lead to novel therapeutic targets for the treatment and prevention of breast and prostate cancer.



Wen Xie, shown in his office at the University of Pittsburgh, has collaborated with NIEHS Cell Biology Group Principal Investigator Anton Jetten on research involving the nuclear receptor ROR and its crosstalk with LXR. (Photo courtesy of Wen Xie and the University of Pittsburgh)

Xie, whose work is partially funded by two NIEHS grants, is an associate professor and interim director for the Center for Pharmacogenetics at the University of Pittsburgh School of Pharmacy. He has published numerous papers on nuclear receptors,

including pregnane X receptor (PXR), constitutive androstane receptor (CAR), retinoid-related orphan receptor (ROR), glucocorticoid receptor (GR) and LXR and their role in gene regulation of enzymes related to hormonal homeostasis, disease states and cancers.

LXR is one of the orphan nuclear receptors that were identified by sequence homology with other nuclear receptors. They were termed "orphans" because their ligands and physiological roles were unknown when the receptors were cloned. As ligand-dependent transcriptional factors, the orphan receptor members act like sensors. When one of its ligands binds to a receptor, the activation process begins with gene induction as a downstream result.

Previously, scientists viewed members PXR and CAR as associated only with xenobiotic ligands and inducing phase I and II drug metabolizing enzyme and drug transporter genes involved with handling drug and other xenobiotic metabolism. Some ligands for LXR, FXR and GR were considered endogenous compounds. The genes they induced are involved in physiological homeostasis such as lipogenesis, cholesterol metabolism, and inflammation, in the case of LXR. With more recent work by Xie and others, this view has changed. Individual orphan nuclear receptor members are no longer limited to the role of inducing genes handling either xenobiotic or endobiotic compounds, but can exhibit crosstalk by inducing genes that handle both types of compounds.

Xie presented data showing that LXR affected estrogen homeostasis by regulating the expression of the estrogen sulfotransferase (EST or SULT 1E1), a phase II drug-metabolizing enzyme in the liver. This enzyme sulfonates estrogen, preventing it from binding to and activating the estrogen receptor. A separate study showed that LXR activated another sulfotransferase isoform, hydroxysteroid sulfotransferase SULT2A1 which Xie showed was "necessary and sufficient to deactivate androgens" by preventing binding to their hormone receptors. Serum levels of estrogen or the androgen steroid testosterone were reduced along with their respective hormonal deactivation.

Estrogens and androgens are risk factors for breast cancer and prostate cancer, respectively. Blocking or reducing estrogen activity has been effective in treating and preventing breast cancer. Similarly, reducing androgen levels reduces the growth of androgen-dependent prostate cancer cells. With its ability to reduce estrogen and androgen levels through activating sulfotransferases, LXR is a potential therapeutic target for treating and preventing breast and prostate cancer.

Engineering Mice to Measure LXR

Xie's work utilized transgenic mice created by his group in order to study the in vivo roles of LXR. In wild type mice, the α isoform of LXR is found in various tissues but is highest in the liver. To make the transgenic mouse, the VP16 activation domain of the herpes simplex virus was fused to the amino terminal of mouse LXRα using the rat liver fatty acid-binding protein (FABP) as its promoter. Named VP-LXRα, this fusion transgene has the same DNA binding specificity as in wild type mice but had much higher constitutively expressed LXR responsive genes. Together with the LXRα and LXRß double knock-out mice and the use of LXR agonists, Xie's group was able to manipulate LXR activation to always off, always on or inducible, which facilitated manipulation of sulfotransferase levels in mice. The VP-LXRα transgenic mouse was also used as a model to examine LXR modulation of bile acid levels and the resulting effects in the liver.

Citation: Peet DJ, Turley SD, Ma W, Janowski BA, Lobaccaro JM, Hammer RE, Mangelsdorf DJ. 1998 Cholesterol and bile acid metabolism are impaired in mice lacking the nuclear oxysterol receptor LXR alpha. Cell 93(5):693-704.

Xie's LXR studies show that this nuclear receptor can be involved in xenobiotic and endobiotic metabolism which can affect hormone levels by inducing phase II metabolizing genes. Crosstalk among the orphan nuclear receptor family members has implications for drug-drug interactions. Xenobiotic as well as endobiotic ligands have the potential to modulate homeostasis of cholesterol metabolism, inflammation, development, insulin response and hormones by activating these receptors. As Xie explained, "What happens in the liver can have effects in breast tissue."

(Laura Hall is a biologist in the NIEHS Laboratory of Pharmacology.)

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Research Finds Novel Roles for AhR in Development

By Brian Chorley

A recent study reports on novel roles for the cellular environmental sensor aryl hydrocarbon receptor (AHR). Using a combination of sophisticated molecular and bioinformatic techniques, an NIEHS-funded research group demonstrated that AHR mediates several biological pathways involved in development and growth in the absence of pollutant stimulation. The study appeared in press online in *Environmental Health Perspectives*.

The findings of this study add to the mounting evidence supporting the idea that pollutant exposure during embryonic development may have serious developmental consequences. "Exposure to AHR ligands during embryonic life may derail the concerted expression of developmental genes," the researchers concluded, "and in addition alter the normal patterns of epigenetic modifications of these genes, an effect that might persist throughout the life-time of the organism and possibly be a determinant of disease susceptibility in the adult."

In the study's conclusion, Puga, above, and colleagues called for interdisciplinary approaches to the epigenetic implications of their findings. "Understanding adult environmental disease may require the synergistic interaction of toxicology and developmental biology." (Photo courtesy of Alvaro Puga)

Alvaro Puga, Ph.D., professor of environmental health and deputy director of the Center for Environmental Genetics at the University of Cincinnati, was principal investigator on the study. Maureen Sartor, Ph.D., who is now a University of Michigan School of Public Health research assistant professor, was lead author on the study.

AHR is a well-studied transcription factor known to respond to environmental pollutants, such as dioxins and polychlorinated biphenyls (PCBs), and mediate expression of genes involved in metabolism and detoxification of these compounds. Additionally, many natural ligands for AHR activation are known, including dietary carotenoids found in fruits and vegetables.

AHR is generally considered an inactive, yet poised, state in the absence of its ligands. However, there is both evolutionary and genetic evidence that AHR is involved in biological mechanisms beyond the breakdown of exogenous chemicals. According to the study, mice with targeted loss of AHR exhibit metabolism-independent, age-related problems with the cardiovascular system, eye and liver. Also, invertebrate forms of AHR have

known roles in development, such as neuron formation in *C. elegans* and appendage morphogenesis in *Drosophila*. Direct environmental response by AHR is only known to exist in vertebrates, but some scientists believe that developmental roles seen in invertebrates may have been conserved through evolution.

In this study, the authors examined gene expression and AHR genomic binding patterns in cultured mouse liver cancer cells that were both exposed and unexposed to chemical pollutants. To assess the genome-wide binding patterns of AHR, a technique known as ChIP-chip was utilized. As anticipated, the analysis revealed AHR binding to several regulatory regions of genes involved in chemical metabolism and detoxification after exposure, although several unrelated regions were bound in unexposed cells. These regions were associated with genes that direct nervous system, eye and blood vessel development, among other developmental and growth processes.

Lead author Sartor earned her doctorate at the University of Cincinnati before joining the computational medicine biology faculty at the University of Michigan School of Public Health. (Photo courtesy of Maureen Sartor)

To corroborate the binding data, global gene expression patterns were examined using microarray gene expression analysis. The results revealed AHR mediation of many genes involved in developmental processes whose regulatory genomic regions were also bound by AHR in the unexposed state.

The study proposed an important distinction between AHR-mediated regulation between the exposed and unexposed state. Specifically, when AHR was "activated" by pollutant exposure, the enriched binding and expression of genes involved in development waned, as genes involved in metabolism were enriched. This highlights a dual, seemingly mutually exclusive role for AHR.

The research team found that AHR-mediated gene patterns significantly shift from roles of homeostasis to exogenous chemical response after pollutant exposure. The investigators hope to broaden their study to other tissues and organs, where they expect to find both overlapping and unique gene networks governed by steady-state and activated AHR.

Citation: Sartor MA, Schnekenburger M, Marlow JL, Reichard JF, Wang Y, Fan Y, Ma C, Karyala S, Halbleib D, Liu X, Medvedovic M, Puga A. 2009. Genome-wide analysis of aryl hydrocarbon receptor binding targets reveals an extensive array of gene clusters that control morphogenetic and developmental programs. Environ Health Perspect doi:10.1289/ehp.0800485

(Brian Chorley, Ph.D., is a postdoctoral fellow in the NIEHS Laboratory of Molecular Genetics Environmental Genomics Group.)

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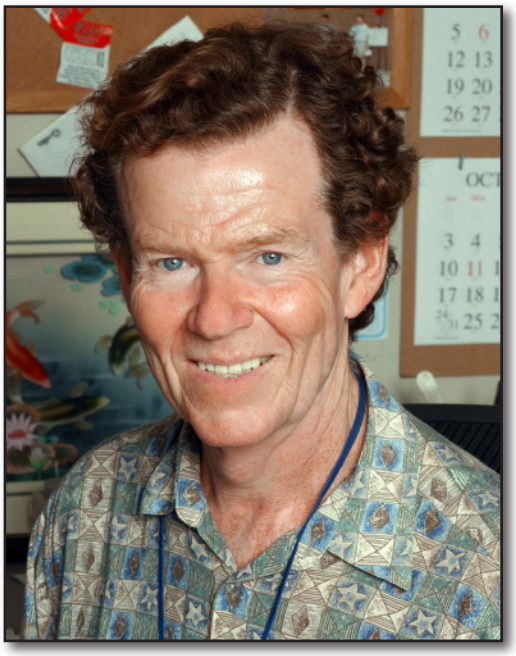
Well Water Should Be Tested Annually to Reduce Health Risks to Children

By Robin Mackar

Private well water should be tested yearly, and in some cases more often, according to new guidance offered by the American Academy of Pediatrics (AAP). Researchers at NIEHS took a lead role in working with the AAP to develop these recommendations and draft a new AAP policy statement about the things parents should do if their children drink well water.



Lead author Walter Rogan (Photo courtesy of Steve McCaw)

The recommendations call for annual well testing, especially for nitrate and microorganisms such as coliform bacteria, which can indicate that sewage has contaminated the well. The recommendations point out circumstances when additional testing should occur, including testing when there is a new infant in the house or if the well is subjected to structural damage.

"Children are especially vulnerable to waterborne illnesses that may come from contaminated wells," said Walter J. Rogan, M.D., an epidemiologist at NIEHS and lead author on the policy statement and technical report that appears in the June issue of Pediatrics. The new policy statement, "Drinking Water from Private Wells and Risks to Children," offers recommendations for inspection, testing and remediation of wells providing drinking water for children.

"With few exceptions, well owners are responsible for their own wells," said Rogan. Private wells are not subject to federal regulations and are only minimally regulated by states. With proper care, well water is safe; however, wells can become contaminated by chemicals or pathogenic organisms.

Nitrate, which comes from sewage or fertilizer, is the most common contaminant in wells. The presence of nitrates can be a problem particularly for infants under three months who can not metabolize nitrate. Water with a nitrate concentration of more than 10 milligrams per liter should not be used to prepare infant formula or given to a child younger than one year. The policy statement suggests using bottled water for infants when nitrate contamination is detected or when the source of drinking water is not known.

The policy statement and accompanying technical report point out that water contamination is inherently local, and that families with wells need to keep in contact with state and local health experts to determine what should be tested in their community. For example, some parts of the country may have arsenic, radon, salt intrusion or agricultural runoff that may get into the water supply.

"As people move out of urban and suburban areas into areas that are not reached by municipal water supplies, it is more important than ever that people know who to contact in their local health department to get information about local groundwater conditions," said N. Beth Ragan of NIEHS, who served as a consultant on these reports. A compilation of state-by-state telephone and Web-based resources of local experts is included in the technical report. Approximately one-sixth of U.S. households now get their drinking water from private wells.

NIEHS Director Linda Birnbaum, Ph.D., says she is pleased that NIEHS researchers took the lead in writing this statement, and continue their longstanding liaisons with the American Academy of Pediatrics to develop state-of-the-science technical reports that can have a direct impact on public health.

"This statement will be extremely useful to many audiences — especially pediatricians," Birnbaum said. "Pediatricians needed a one-stop shopping document that they can share with parents who have concerns about their children's sources of drinking water."

Citations: Rogan WJ, Brady MT, the Committee on Environmental Health and the Committee on Infectious Diseases. 2009. Technical Report. Drinking Water from Private Wells and Risks to Children. Pediatrics 123:6. DOI: 10.1542/peds2009-0751.

Committee on Environmental Health and Committee on Infectious Diseases. Policy Statement. 2009. Drinking Water from Private Wells and Risks to Children. Pediatrics123:6. DOI: 10.1542/peds2009-0751.

(Robin Mackar is the news director in the NIEHS Office of Communications and Public Liaison and a regular contributor to the Environmental Factor.)

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Possible Link Between Childhood Obesity and Allergies

By Robin Mackar

A new study indicates there may be yet another reason to reduce childhood obesity — it may help prevent allergies. The study published in the May issue of the Journal of Allergy and Clinical Immunology showed that obese children and adolescents are at increased risk of having some kind of allergy, especially to a food. The study was funded by the National Institute of Environmental Health Sciences (NIEHS) and the National Institute of Allergy and Infectious Diseases (NIAID), both parts of the National Institutes of Health.

Principal Investigator Darryl Zeldin (Photo courtesy of Steve McCaw)

"We found a positive association between obesity and allergies," said Darryl Zeldin, M.D., acting clinical director at NIEHS and senior author on the paper. The researchers analyzed data on children and young adults ages 2 to19 from a new national dataset designed to obtain information about allergies and asthma. "While the results from this study are interesting, they do not prove that obesity causes allergies. More research is needed to further investigate this potential link," Zeldin said.

The study is the first to be published using new data from the National Health and Nutrition Examination Survey (NHANES). NHANES is a large nationally representative survey conducted by the National Center for Health Statistics, a part of the Centers for Disease Control and Prevention. NHANES is designed to assess the health and nutritional status of adults and children in the United States. An allergy/asthma component was supported by NIEHS and added to the 2005-2006 NHANES study, making it the largest nationally representative dataset of allergy and asthma information ever assembled in the United States.

"We have all the pieces of the puzzle in this dataset," said Zeldin. "The allergy and asthma component of NHANES provides allergen exposure information, allergic sensitization information, as well as disease outcome information. There is a wealth of knowledge we will be able to gain by analyzing these data that will be useful to allergy and asthma sufferers."

In this study, the researchers analyzed data from 4,111 children and young adults aged 2–19 years of age. They looked at total and allergen-specific immunoglobulin E (IgE) or antibody levels to a large panel of indoor, outdoor and food allergens, body weight, and responses to a questionnaire about diagnoses of hay fever, eczema, and allergies. Obesity was defined as being in the 95th percentile of the body mass index for the child's age. The researchers found the IgE levels were higher among children who were obese or overweight. Obese children were about 26 percent more likely to have allergies than children of normal weight.

Coauthor Stephanie London (Photo courtesy of Steve McCaw)

"The signal for allergies seemed to be coming mostly from food allergies. The rate of having a food allergy was 59 percent higher for obese children," said NIEHS researcher Stephanie London, M.D., a co-author on the study.

"As childhood obesity rates rise, NIEHS will continue to work to determine how environmental factors affect this epidemic," said Linda Birnbaum, Ph.D., NIEHS director. "Seeing a possible link between obesity and allergies provides additional motivation for undertaking the challenge of reducing childhood obesity."

"Given that the prevalence of both obesity and allergic disease has increased among children over the last several decades, it is important to understand and, if possible, prevent these epidemics," said Cynthia M. Visness, Ph.D., lead author on the paper and a scientist at Rho Federal Systems Division, Inc. in Chapel Hill, N.C.

First author Cynthia Visness (Photo courtesy of Cynthia Visness)

Citation: Visness CM, London SJ, Daniels JL, Kaufman JS, Yeatts KB, Siega-Riz AM, Liu AH, Calatroni A, Zeldin DC. 2009. Association of obesity with IgE levels and allergy symptoms in children and adolescents: Results from the National Health and Nutrition Examination Survey 2005-2006. J Allergy Clin Immunol 123(5):1163-1169. Doi:10.1016/j.jaci.2008.12.1126.

(Robin Mackar is the News Director in the NIEHS Office of Communications and Public Liaison and a regular contributor to the *Environmental Factor*.)

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Expert Panel Reviews New Local Lymph Node Assay for Product Testing

By Debbie McCarley

An international scientific peer review panel of 15 expert scientists met on April 28-29 on the NIH Bethesda campus to review new test methods proposed to determine if chemicals and substances may cause allergic contact dermatitis. The panel was convened by the National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) and the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM).

Stokes, center, makes a point about the tests, while Wind, left, looks on and Luster, right, makes notes. (Photo courtesy of Ernie Branson and NIH)

The panel reviewed three new versions of the murine local lymph node assay (LLNA) and proposals to use the LLNA to test pesticide formulations and other products. Federal agencies accepted the LLNA in 1999 for safety testing, based on ICCVAM recommendations that the LLNA was a valid substitute for the traditional guinea pig test methods used to identify potential sensitizers. The LLNA has many advantages, including using fewer animals, eliminating the potential discomfort that can occur with positive results in the guinea pig methods and providing dose-response information. The LLNA can be completed in one week, as compared to four weeks for the guinea pig test.

Panel participants gathered in the NIH Natcher Auditorium. Front row, left to right — Lovell, Luster, Wind, Olson, Jirova, and Stokes. Second row, left to right: Richmond, Api, Ullrich, Flournoy and Theran. Top row — Yoshida, Regal, Maibach, and Alepee. Woolheiser was not pictured. (Photo courtesy of Ernie Branson and NIH)

Unlike the original LLNA, the three new versions use nonradioactive markers to measure lymphocyte proliferation. One of them measures increases in ATP content, while the other two measure the incorporation of bromodeoxyuridine (BrdU) by either ELISA or flow cytometry. Two of the methods were developed in Japan, while the BrdU-ELISA method was developed through an NIEHS Small Business Innovation Research grant with MB Research Laboratories in Pennsylvania.

The panel evaluated the validation status of each of the proposed alternative test methods and applications according to established federal and international criteria. The panel also commented on draft ICCVAM recommendations regarding the usefulness and limitations of each proposed test method and application.

The Panel agreed that two of the three nonradioactive LLNA procedures reviewed could be used to identify substances as potential skin sensitizers or nonsensitizers, with certain limitations. The Panel supported the third

method, contingent upon demonstration of adequate interlaboratory reproducibility in at least two other labs and a laboratory data audit to verify the summary data submitted for review. The Panel also concluded that the LLNA should be able to test any material, including pesticides and substances such as fragrances and dyes, unless the substance is thought to have properties that would interfere with the conduct or accuracy of the assay.

Acceptance by federal agencies of a nonradioactive version of the LLNA that can be applied to a broader range of chemicals and products should permit more widespread use of the LLNA, further reduce the number of animals needed and reduce animal discomfort associated with the guinea pig tests. The avoidance of radioactive materials will also provide a benefit to the environment. ICCVAM, which has members from 15 federal agencies, coordinates the technical evaluations of new, revised and alternative methods for regulatory safety testing of chemicals and products. ICCVAM will consider the Panel's report, along with comments from the public and its scientific advisory committee in preparing final test method recommendations that will be forwarded to federal agencies later this year.

The goal of NICEATM and ICCVAM is to achieve the regulatory acceptance of alternative test methods that will benefit animal welfare by reducing, refining and replacing animal use — the *3Rs* of alternative testing — and benefit public health by ensuring continued or improved protection of human and animal health and the environment.

(Debbie McCarley is the Special Assistant to Rear Admiral William Stokes, D.V.M., D.A.C.L.A.M., director of the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods.)

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Key Figures in the Interagency Expert Panel Review

An ICCVAM Immunotoxicity Working Group (IWG) developed draft LLNA recommendations and draft Background Review Documents for review by the Panel with support from NICEATM. Abby Jacobs, Ph.D., of the Food and Drug Administration and Joanna Matheson, Ph.D., of the Consumer Product Safety Commission co-chaired the IWG.

The IWG includes scientists from the Consumer Product Safety Commission, the U.S. Environmental Protection Agency, the Food and Drug Administration, the National Institute for Occupational Safety and Health and NIEHS. NIEHS scientists Dori Germolec, Ph.D., William Stokes, D.V.M., and Raymond Tice, Ph.D., participated on the IWG. Stokes is director of NICEATM and executive director of ICCVAM. Marilyn Wind, Ph.D., of the Consumer Product Safety Commission, is the chair of ICCVAM.

The panel was chaired by Michael Luster, Ph.D., who recently retired from the National Institute for Occupational Safety and Health after serving for many years as a branch chief. The panel included scientists with expertise in immunotoxicology, clinical immunology, biostatistics, regulatory toxicology, occupational health and animal welfare science.

Former NIEHS postdocs David Lovell, Ph.D., a biostatistician in the Medical School at the University of Surrey in the U.K., and Michael Olson, Ph.D., director of Occupational Toxicology for GlaxoSmithKline, served on the panel, as did Takahiko Yoshida, M.D., Ph.D., a Professor at the Asahikawa Medical College in Japan and a former guest researcher at NIEHS.

Additional panelists included Nathalie Alépéé, Ph.D., of L'Oreal; Anne Marie Api, Ph.D., of the Research Institute for Fragrance Materials; Nancy Flournoy, Ph.D., of the University of Missouri – Columbia; Dagmar Jírová, M.D., Ph.D., of the Czech Republic National Institute of Public Health: Howard Maibach, M.D., of the University of California, San Francisco; Jean Regal, Ph.D., of the University of Minnesota – Duluth Campus Medical School; Jon Richmond, M.B. Ch.B., of the U.K. Home Office; Peter Theran, V.M.D., of the Masachusetts Society for the Prevention of Cruelty to Animals; Stephen Ullrich, Ph.D., of the University of Texas M.D. Anderson Cancer Center; and Michael Woolhiser, Ph.D., Dow Chemical Company.

This Month in EHP

By Eddy Ball

The June 2009 issue of *Environmental Health Perspectives* is now available online, with a feature story on the growing problem of antibiotic resistance and the emergence of new strains of bacteria. The journal also takes a critical look at the aquaculture industry's impact on the environment as increasing demand for fish leads to the proliferation of fish farms.

A new study surveys modern environmental health hazards in Africa, and a team of researchers led by NIEHS scientist Retha Newbold reports on ovarian pathology in offspring of mice exposed to bisphenol A (BPA) during gestation. In a study of rats exposed to low levels of organophosphate insecticides, researchers discover a possible link between diet and neurodevelopment effects of pesticide exposure. Other new studies address semen quality in young Danish men and perfluoroalkyl acids exposure, the effects of wildfire particulate matter on lung function in mice, and the association between specific pesticides with PCBs and childhood leukemia.

- **The Landscape of Antibiotic Resistance** — Looking at the possibilities for reducing or resolving this growing threat to public health
- **Aquaculture Navigates Through Troubled Waters** — Weighing the environmental costs of farm-raised fish that are prized for their polyunsaturated fatty acid content
- **Modern Environmental Health Hazards (MEHHs) in Africa** — Forecasting the health impact of unmitigated environmental exposures on a population already burdened by poverty, malnutrition and HIV/AIDS
- **Long-Term Effects of Prenatal BPA on the Mouse Reproductive Tract** — Offering more evidence of developmental anomalies in offspring linked to maternal exposures during pregnancy
- **High-Fat Diet May Offset Developmental Effects of Parathion** — Exploring the link between effects of developmental neurotoxicants and dietary modification in adult rats
- **PFAAs and Semen Quality in Young Men** — Reporting that Danish recruits with the highest semen levels of perfluoroalkyl acids had dramatically reduced sperm counts
- **Toxicity of Particulate Matter from California Wildfires** — Comparing the lung's response to particulate matter collected from ambient air during wildfires and response to normal ambient air particulate matter concentrations from the same region
- **Organochlorines and Childhood Leukemia** — Linking exposures to PCB congeners in home carpet dust to increased incidence of childhood leukemia, with a stronger association found among non-Hispanic whites than among Hispanics

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Upcoming Distinguished Lecturer Harinder Singh

By Eddy Ball

NIEHS will welcome the next speaker in its 2008-2009 Distinguished Lecture Series on June 9 at 11:00 in Rodbell Auditorium. Harinder Singh, Ph.D., will discuss "Gene Regulatory Networks Orchestrating Innate and Adaptive Immune Cell Fates" in a lecture hosted by Principal Investigator Paul Wade, Ph.D., of the NIEHS Eukaryotic Transcriptional Regulation Group.

Distinguished Lecturer Harinder Singh (Photo courtesy of the University of Chicago)

Singh is the Louis Block Professor in the Department of Molecular Genetics and Cell Biology and a Howard Hughes Medical Institute (HHMI) investigator at the University of Chicago. His research interests include studying the molecules that control the development of different immune cells during hematopoiesis — the formation and development of blood cells — to better understand the networks of interconnected transcription factors, signaling molecules and miRNAs that regulate cell fate choice and developmental transitions.

Recent work in Singh's lab has focused on the ways that gene positioning in the nucleus affects gene expression. According to Singh, a more complete characterization of the molecular mechanism that cells use to position genes could one day help scientists develop interventions to take advantage of this process to manipulate the expression of genes involved in immune system diseases and even cancer.

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ATS Calls for 2010 Conference Proposals

By Eddy Ball

The American Thoracic Society (ATS) has announced a "Call for Input" for planning the program of its international conference, ATS 2010, scheduled May 14–19, 2010 in New Orleans. The organization encourages suggestions for the program in all aspects of pulmonary, critical care and sleep medicine. The deadline for proposals is June 30, 2009.

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ATS has sent up a special Call-for-Input Web site, where proposal submissions must be submitted online. The site includes proposal requirements and offers guidance for submission.

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Extramural Update

The SRP Announces 2009 New Awards

In April 2009 the NIEHS Superfund Research Program (SRP) announced three new multi-year program grant awards: Brown University, the University of Washington (UW) and Oregon State University (OSU). Each of these grants is comprised of complementary projects, which are thematically related around an environmental health hazard of interest.

The SRP is a network of university grants designed to seek solutions to the complex health and environmental issues associated with the nation's hazardous waste sites. The research conducted by the SRP is a coordinated effort with the Environmental Protection Agency (EPA), which is the federal entity charged with cleaning up the worst hazardous waste sites, designated as Superfund sites, in the country.

The Duwamish River near Seattle is one of the sites that UW SRP researchers will study with the renewed grants. (Photo courtesy of the Duwamish River Cleanup Coalition)

These projects encompass the spectrum of environmental health research, including field studies and site remediation, exposure assessment, toxicology and human health studies, and remediation technology development. In addition, each grant funds "cores," supporting auxiliary functions that include grant administration, student training and development, and community outreach and research translation.

The SRP at Brown has been recognized for its innovative community outreach and involvement programs. (Photo courtesy of Brown University)

OSU will be studying the effects of polycyclic aromatic hydrocarbons (PAHs) on human health, with an emphasis on special populations that experience higher rates of exposure. Researchers will also be conducting atmospheric fate and transport studies to determine the origins of PAHs found on the west coast of the United States. Light and heat stable, PAHs are capable of attaching themselves to other particles and traveling thousands of miles in the air to settle in lakes and rivers as far as continents away from their origin. Researchers will collect samples from China, Japan and Oregon to determine personal exposure loading and the origins of PAH exposure in the United States.

Brown University's program will continue to examine land reuse and complex exposures in the densely populated state of Rhode Island. Researchers will address further the theoretical and practical aspects of disease mechanisms and potential biomarkers associated with exposures to complex mixtures, as well as the identification, separation and remediation of these mixtures in the environment. Brown's program features a

cooperative academic-government-community effort to address scientific and research translation issues (see archived story). In its previous grant, the Brown researchers made a significant contribution to the passage of state legislative measures to protect people from exposure.

UW investigators will continue their research of biomarkers to determine early indicators of damage and exposure to neurotoxicants and pesticides. They are developing and validating biomarkers for characterizing neurotoxicity mechanisms and risk to humans, animals and the environment. In addition, they are studying methods for modifying exposure/risk relations and implementing phytoremediation techniques (see archived story).

New Name for Superfund

Beginning June 1, 2009, the NIEHS Superfund Basic Research Program will have an updated and shorter name: **"Superfund Research Program."** The new URL is http://www.niehs.nih.gov/srp. Please take a moment to bookmark this new web address.

The SRP congratulated Brown University and the University of Washington (UW) on their successful recompetition and welcomed Oregon State University (OSU) as a newly funded program.

Contact: William Suk, Ph.D. director, SRP

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Extramural Papers of the Month

By Jerry Phelps

- Alzheimer's Disease Linked to Mitochondrial Damage
- Swine Flu Susceptibility Linked to Arsenic Exposure
- Gene May Be Linked to Lung Cancer
- Phthalate Exposure May Extend Pregnancy

Read the current Superfund Research Program Research Brief. New issues are published on the first Wednesday of each month.

Alzheimer's Disease Linked to Mitochondrial Damage

New research findings suggest that preventing S-nitrosylation of the mitochondrial protein Drp1 by the free radical nitric oxide may reduce or even prevent neurodegeneration in Alzheimer's patients.

The NIEHS-supported research team found that S-nitrosylated Drp1facilitates mitochondrial fragmentation, which leads to synaptic injury and eventual nerve cell death. This finding helps to explain how beta-amyloid protein causes neurodegeration. Beta-amyloid protein is the source of the nitric oxide, which reacts with Drp1. By identifying Drp1 as the protein responsible for the synaptic injury, the investigators have discovered a new target for developing drugs that may stop or slow the progression of Alzheimer's.

Drp1 is an enzyme that mediates fission or fragmentation of mitochondria. The team showed that excessive nitric oxide production caused damage to Drp1 which leads to excessive mitochondrial fragmentation in cultured nerve cells. Elevated levels of S-nitrosylated Drp1 were also found in the brains of Alzheimer's patients, but not in those with Parkinson's disease or controls who didn't have neurodegenerative disease, adding additional evidence to the *in vitro* findings.

Finally, experiments to decrease Drp1 activity, either using RNA interference or a mutation that prevented Drp1 activity, inhibited excess mitochondrial damage and protected the neurons. These findings suggest that drugs or interventions to prevent damage to Drp1could prove to be effective prevention or treatment strategies for Alzheimer's disease.

Citation: Cho DH, Nakamura T, Fang J, Cieplak P, Godzik A, Gu Z, Lipton SA. 2009. S-nitrosylation of Drp1 mediates beta-amyloid-related mitochondrial fission and neuronal injury. Science 324(5923):102-105.

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Swine Flu Susceptibility Linked to Arsenic Exposure

Low-level exposure to arsenic at concentrations found commonly in U.S. drinking water compromises the initial immune response to H1N1 or swine flu infection according to NIEHS-supported scientists. The study, conducted in laboratory mice, suggests that people exposed to arsenic in their drinking water may be at increased risk for more serious illness or death in response to infection from the virus.

The arsenic-exposed mice initially showed a weak immune response to the virus, and when the immune response fully developed, it was "too robust and too late," according to the study's senior author, Josh Hamilton. The late influx of immune cells to the lung and the inflammatory response caused lung damage and bleeding not seen in the control animals. Over the course of the infection, the death rate in arsenic-exposed animals was much higher than the non-exposed mice.

The current U.S. EPA drinking water standard is 10 parts per billion; however, 100 parts per billion levels are commonly found in well water in areas where arsenic is geologically abundant such as New England, Florida, large portions of the Midwest, the Southwest and the Rocky Mountains. The authors also point out that high levels of arsenic in drinking water are common in the areas of Mexico where swine flu was initially reported.

Citation: Kozul CD, Ely KH, Enelow RI, Hamilton JW. 2009. Low dose arsenic compromises the immune response to influenza A infection *in vivo*. Environ Health Perspect. doi: 10.1289/ehp.0900911

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Gene May Be Linked to Lung Cancer

Recent research from the Environmental Health Sciences Center at the University of Cincinnati indicates that a gene found on chromosome 6 known as RGS17 may be a lung cancer susceptibility gene. The researchers found a significant association between three single nucleotide polymorphisms in the gene and lung cancer susceptibility. These results were confirmed in two separate familial lung cancer populations with a combined total of 380 lung cancer cases and 638 controls.

In addition to the human studies, transgenic mouse experiments were conducted as well. The animal studies showed inhibition of lung tumor cell proliferation and the development of tumors in mice when RGS17 gene expression was decreased.

Cigarette smoking is the number one cause of lung cancer. However, only 15-18 percent of heavy smokers develop lung cancer and some people who never smoke develop the disease. These studies point to a genetic link that may help to explain both phenomena and could lead to new prevention strategies to decrease the occurrence of lung cancer and to identify people who are at increased risk of developing the disease.

Citation: You M, Wang D, Liu P, Vikis H, James M, Lu Y, Wang Y, Wang M, Chen Q, Jia D, Liu Y, Wen W, Yang P, Sun Z, Pinney SM, Zheng W, Shu XO, Long J, Gao YT, Xiang YB, Chow WH, Rothman N, Petersen GM, de Andrade M, Wu Y, Cunningham JM, Wiest JS, Fain PR, Schwartz AG, Girard L, Gazdar A, Gaba C, Rothschild H, Mandal D, Coons, T, Lee J, Kupert E, Seminara D, Minna J, Bailey-Wilson JE, Amos CI, Anderson MW. 2009. Fine mapping of chromosome 6q23-25 region in familial lung cancer families reveals RGS17 as a likely candidate gene. Clin Cancer Res 15(8):2666-2674.

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Phthalate Exposure May Extend Pregnancy

A multi-state epidemiologic study, funded in part by NIEHS, reports that women at the upper range of exposure to the plasticizing agent di-(2-ethylhexyl) phthalate (DEHP), had a two day longer gestation than women at the lower range of exposure. The highly exposed women also had higher odds for caesarian section delivery and delivery at 41 weeks of gestation or later, as well as decreased odds for preterm delivery. These findings suggest that DEHP may interfere with the hormonally controlled signaling that initiates birth.

Phthalates are used in a wide variety of products including food and beverage containers, pharmaceutical pills and nutritional supplements, gelling agents, personal care products, medical devices, detergents, children's toys and nail polish. As of 2004, manufacturers produced 800 million pounds of phthalates each year.

When added to plastics, phthalates allow the long polyvinyl molecules to slide against one another. Phthalates are easily released into the environment because there is no covalent bond between the phthalates and plastics in which they are mixed. As plastics age and break down, the release of phthalates accelerates. Because phthalates are subject to biodegradation, photo-degradation and anaerobic degradation, they do not generally persist in the outdoor environment.

Citation: Adibi JJ, Hauser R, Williams PL, Whyatt RM, Calafat AM, Nelson H, Herrick R,Swan SH. 2009. Maternal urinary metabolites of di-(2-ethylhexyl) phthalate in relation to the timing of labor in a US multicenter pregnancy cohort study. Am J Epidemiol 169(8):1015-1024.

(Jerry Phelps is a program analyst in the NIEHS Division of Extramural Research and Training. Each month, he contributes summaries of extramural papers to the *Environmental Factor*.)

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Intramural Papers of the Month

By Robin Arnette

- Urate May Protect Against Parkinson's Disease
- Cholesterol-Rich Microdomains Play Crucial Role in MEK-ERK Pathway
- SIRT1 May Prevent Obesity-Associated Diseases
- A New Algorithm for Protein Binding Site Analysis

Urate May Protect Against Parkinson's Disease

NIEHS researchers have found that a higher concentration of urate in the blood was associated with a lower risk of Parkinson's disease. Previous studies from other research groups suggested that urate offered a protective effect against Parkinson's disease among Caucasian men, but data on Caucasian women and other ethnic groups were lacking.

The study population included 15,036 volunteers of the Atherosclerosis Risk In Communities (ARIC) cohort, a twenty-year long, biracial and population-based study that included 55 percent women and 27 percent African Americans. These participants were recruited from four communities in the U.S. between 1987 and 1989 and have since been followed with three triennial visits and annual surveillance.

In this study, the plasma concentration of urate measured at baseline was inversely associated with Parkinson's risk. The association was clear for Caucasian men and was also suggested for Caucasian women and African Americans. Since oxidative stress destroys the dopaminergic neurons in the substantia nigra, scientists theorized that urate — a potent endogenous antioxidant — removes reactive nitrogen and oxygen radicals and thus prevents neuronal loss.

Citation: Chen H, Mosley TH, Alonso A, Huang X. 2009. Plasma urate and Parkinson's disease in the Atherosclerosis Risk in Communities (ARIC) study. Am J Epidemiol 169(9):1064-1069.

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Cholesterol-Rich Microdomains Play Crucial Role in MEK-ERK Pathway

Lipopolysaccharide (LPS), an initiator of the macrophage innate immune response, triggers downstream signaling by recruiting and activating proteins in lipid rafts — cholesterol-rich membrane microdomains. NIEHS investigators have determined that raft compartmentalization regulates proteasome activity in activation of the MEK-ERK pathway.

Previous reports suggested an essential role for proteasomal degradation of IκB kinase-phosphorylated p105 in LPS activation of ERK mitogen-activated protein kinase, so the research team used quantitative proteomics to analyze macrophage detergent-resistant membrane (DRM) raft isolates during LPS exposure to identify a role for rafts in organizing these events.

The research team uncovered the following results:

- The LPS signaling cascade from proteasomal degradation of p105 to ERK activation occurs in rafts and requires raft integrity.
- LPS alters the complement of 26S proteasome subunits in rafts, selectively activating the proteasome within this subcellular compartment. This report is the first publication to directly demonstrate proteasome function within rafts.

This work provides evidence that proteasome subunits localize to rafts, organize within rafts following LPS exposure, and experience functional changes in activity during LPS signaling.

Citation: Dhungana S, Merrick BA, Tomer KB, Fessler MB. 2009. Quantitative proteomics analysis of macrophage rafts reveals compartmentalized activation of the proteasome and of proteasome-mediated ERK activation in response to lipopolysaccharide. Mol Cell Proteomics 8(1):201-213.

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SIRT1 May Prevent Obesity-Associated Diseases

SIRT1, a member of the family of NAD^+-dependent histone deacetylases (HDACs) known as sirtuins, regulates lipid homeostasis in response to nutrient and hormonal signals. The research, performed by NIEHS scientists, showed that a major target of SIRT1 in the liver is the peroxisome proliferators-activated receptor α (PPARα) — a nuclear receptor that mediates the response to fasting and starvation.

Since the liver is the key metabolic organ that regulates lipid metabolism, its dysfunction is responsible for many human illnesses, such as dyslipidemia and fatty liver disease. The research team sought to better understand the mechanisms that control lipid and energy metabolism, with the goal of developing new therapeutic strategies.

The authors demonstrated that specific deletion of hepatic SIRT1 drastically impaired PPARα signaling, while over expression of SIRT1 induced the expression of PPARα targets. When fed a high-fat diet, liver-specific SIRT1 knockout mice developed hepatic inflammation, endoplasmic reticulum stress, and hepatic steatosis — the buildup of fat in liver cells. The findings suggest that therapeutic strategies designed to modulate SIRT1 activity may be helpful in treating hepatic diseases and obesity-associated metabolic syndrome.

Citation: Purushotham A, Schug TT, Xu Q, Surapureddi S, Guo X, Li X. 2009. Hepatocyte-specific deletion of SIRT1 alters fatty acid metabolism and results in hepatic steatosis and inflammation. Cell Metab 9(4):327-338.

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A New Algorithm for Protein Binding Site Analysis

Scientists looking for a faster way to identify motifs in large amounts of sequence data now have a free *de novo* motif discovery tool called GADEM that can do the job. Developed by researchers at NIEHS, GADEM combines word-enumeration with a local expectation-maximization (EM) search technique that employs an efficient search algorithm. It is an extension of the well-known MEME algorithm and is easy to use.

GADEM's initial models are generated from spaced dyads that use over-represented words, usually three to six characters in length, as "seeds." Then, GADEM uses a genetic algorithm (GA) to guide the formation of the spaced dyads from the seeds. When the program was applied to six genome-wide ChIP datasets, which totaled approximately 0.5 to 1 million nucleotides, the expected p53 motif was identified every time. In addition, 15-30 motifs of various lengths were identified in each dataset.

GADEM is a novel *de novo* motif discovery tool that may be applied to large scale sequence data for unbiased motif discovery.

Citation: Li L. 2009. GADEM: A genetic algorithm guided formation of spaced dyads coupled with an EM algorithm for motif discovery. J Comput Biol 16(2):317-329.

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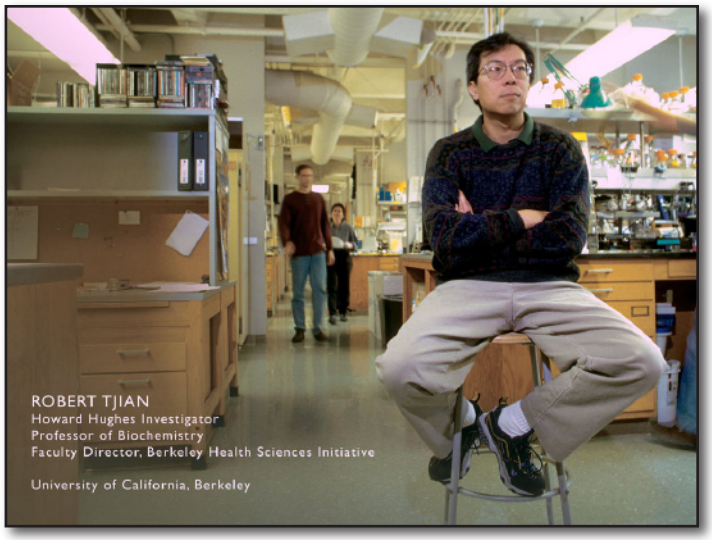
Inside the Institute

Scientific Leader Robert Tjian Speaks at NIH Asian Heritage Event

By Eddy Ball

NIEHS staff were part of the off-site audience as NIH videocast its 2009 Asian/Pacific Islander Heritage Month Observance Program held May 14 in Masur Auditorium on the Bethesda campus. The featured speaker was cell biologist Robert Tjian, Ph.D., who developed the theme of "Leadership in Science — Meeting the Challenges of a Changing World" with reflections on his role as a scientific leader of Asian origin and details of some of his latest findings, which offer new insights into the mechanisms of cell differentiation.



Tjian is shown in lab space at the University of California, Berkeley, following the announcement of a $40 million grant to fund the Li Ka Shing Center for Biomedical and Health Sciences (Photo courtesy of Ben Ailes and the Office of Public Relations at the University of California, Berkeley)

Tjian is the director of the Li Ka Shing Center for Biomedical and Health Sciences at the University of California, Berkeley, where he was a professor from 1987 to 2009, and since April, the president of the Howard Hughes Medical Institute (HHMI). Tjian has moved some of his lab to HHMI's Janelia Farm Research Campus in Virginia and continues research in his lab at Berkeley.

The program, sponsored by the NIH Office of Equal Opportunity and Diversity Management (OEODM) and the NIH Asian American/Pacific Islander Employee Committee, opened with remarks by Lucie Chen, acting NIH Asian program manager. NIH Deputy Director for Intramural Research Michael Gottesman, M.D., then spoke of Tjian as a "role model for the kind of leadership we'd like to develop at NIH." As Gottesman explained, while people of Asian descent are well represented in the ranks of investigators at NIH, making up 24 percent of the total, they occupy only about 5 percent of leadership positions at the branch chief level and above.

Tjian reflected on his own journey from Hong Kong to South America as a child and later to southern New Jersey, where he attended high school. He noted that "when I first came to Berkeley [as a college student], I was probably the only Asian face in my class in biochemistry. Today, if you look at the class, it's probably 67 percent Asian."

Referring to his friend and colleague Steven Chu, Ph.D., the new secretary of the U.S. Department of Energy and a neighbor in Chevy Chase, Md., Tjian said that Chu is "emblematic" of "Asians of many different extractions making great strides in every aspect of American culture."

During the scientific portion of his talk, Tjian presented unpublished findings from experiments in the "highly, highly regulated process" of RNA polymerase transcription — the way cells read DNA, transcribe RNA and trigger the production of proteins. He has studied several cell types, including muscle, neuron, liver and embryonic stem cells, to characterize the signal activator complexes involved in activation.

As the head of HHMI, Tjian oversees the work of more than 350 investigators at 67 universities, medical schools and research organizations across the United States. Founded in 1953 by Howard Hughes, HHMI currently has an endowment of $17.5 billion and has spent more than $8.3 billion over the past two decades on research support, training and education for the nation's top and most promising scientists. Tjian said he is committed to expanding HHMI so it will "have a role internationally as well as nationally."

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Employees Pitch In with Habitat for Humanity Project

By Eddy Ball

Continuing a tradition of community involvement with the non-profit group Habitat for Humanity, members of the NIEHS Division of Extramural Research and Training (DERT) Community Builders group donated an afternoon of their free time in May to help complete one of the final homes in Hope Crossing, the group's first "green" neighborhood in Durham, N.C. The volunteer crew spent a little more than three hours installing vinyl siding on the home and cleaning the cul-de-sac to keep Habitat from receiving a fine from the building inspector.

The DERT crew neared the end of its productive afternoon in the new Habitat for Humanity Hope Crossing community. (Photo courtesy of Roxanne Hall)

All the homes in Hope Crossing feature solar panels on the roof for heating water, rain barrels to collect water from downspouts, energy-efficient appliances, and building materials made from recycled products, including the certified lead-free materials used in the children's playground structures. Reflecting Habitat's dedication to building community as well as infrastructure, the residents of Hope Crossing share a large community garden.

The DERT crew was part of a volunteer labor force working with homeowners in the community, who supply "sweat equity" as part of Habitat's interest-free loan program. Many of the materials are donated — helping ensure that the houses average a very affordable $50,000 each.

Veteran crew member Jerry Phelps attended a home dedication just prior to his shift and said he was gratified to see that the entire neighborhood was on hand — many of the residents having satisfied some of their "sweat equity" by helping construct their new neighbors' home. Phelps and co-worker Heather Henry also had an opportunity to revisit some of the houses they had worked on earlier and see new residents enjoying the fruits of their collective efforts.

As Phelps said afterwards, "It was a fun day in the sun doing something with our hands that will truly make a difference in the lives of a worthy family." Phelps encourages anyone interested in volunteering or contributing to Habitat for Humanity to contact him or former NIEHS employee Roxanne Hall, who now works for Habitat, or visit the group's Web site.

Phelps, who spends his day job analyzing program performance for NIEHS, showed that he could also wield a 22-ounce hammer. (Photo courtesy of Roxanne Hall)

Heather Henry, center, helped an AmeriCorps volunteer measure siding. Liz McNair, right, prepared another section for installation. (Photo courtesy of Roxanne Hall)

Astrid Haugen, left, and Haugen's husband John Stranzl, placed siding as Christie Drew and other DERT volunteers worked elsewhere on the house. (Photo courtesy of Roxanne Hall)

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