

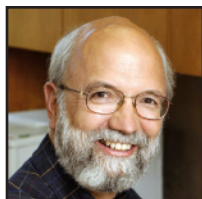


Environmental Factor

Your Online Source for NIEHS News

August 2008

NIEHS Spotlight



Allen Wilcox Honored by University of Bergen

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29, when the University of Bergen will award him an honorary degree. ...[read more](#)



Looking to the Future of Environmental Public Health

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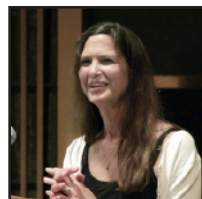
Promoting Hands-on Science in Texas Schools

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NIH Continues Search for NIEHS Director

NIH is now accepting applications from qualified candidates for the position of director of NIEHS. ...[read more](#)

Science Notebook



Cline Explores Circuits in the Developing Brain

The latest NIEHS distinguished lecture in the 2007–2008 series featured Cold Spring Harbor Laboratory professor Hollis T. Cline, Ph.D., and was hosted

by NIEHS Principal Investigator Serena Dudek, Ph.D. Cline presented "Mechanisms of Circuit Development: The Contribution of Synapse Elimination" on July 8 in Rodbell Auditorium. ...[read more](#)



Laboratory of Structural Biology Undergoes Scientific Review

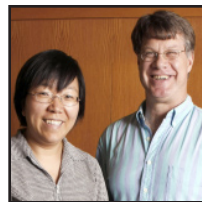
Every four years laboratories at NIEHS meet with their Board of Scientific Counselors (BSC) to ensure that the labs are carrying out sound hypothesis-based research. ...[read more](#)



Epigenetic Changes May Be Early Indicators of Cancer

A recent NIEHS-funded study headed by Stephen B. Baylin, M.D., at The Johns Hopkins Kimmel Cancer Center in Baltimore, Md., adds to the evidence that

mutation and epigenetic phenomena in common genes may be early prognosticators of cancer.[read more](#)



Team Develops Novel Method to Monitor DNA Damage Recognition

In a study published in the June issue of *Nanoletters*, Principal Investigator Bennett Van Houten,

Ph.D., and Postdoctoral Fellow Hong Wang, Ph.D., in the NIEHS Laboratory of Molecular Genetics DNA Repair and Mitochondrial Damage Group, along with their collaborators from the University of North Carolina, present novel methods that overcome obstacles encountered in single-molecule studies. ...[read more](#)

NIEHS Spotlight

Special Focus on Superfund



Superfund Grantee Hammock Honored for Teaching

Veteran Superfund Basic Research Program (SBRP) grantee Bruce Hammock, Ph.D., will receive the 2008 Distinguished Teaching Award for

Graduate and Professional Teaching from the University of California Davis (UCD), where he is a distinguished professor of entomology. ...[read more](#)



Superfund Puts Trust at the Top in Rhode Island Project

An article published in the July 1 issue of *Environmental Science and Technology* by scientists in the Brown University Superfund Basic Research

Program (SBRP) reports on a successful collaboration between a multi-disciplinary research program and community representatives of a contaminated neighborhood in Tiverton, R.I. ...[read more](#)



2008 Green Technology Entrepreneurship Academy Meets

The University of California Davis (UCD) Center for Entrepreneurship hosted the Green Technology Entrepreneurship

Academy (GTEA) 2008 July 7 – 11 in the Tahoe Center for Environmental Sciences at Sierra Nevada College in Incline Village, Nevada.[read more](#)



Science Camp for Border Students

From the outset, almost everything about the very first University of Arizona (UA) summer camp for the environmental sciences held June

16 – 20 was designed to set it apart from the typical summer camp experience. ...[read more](#)

Science Notebook



New Techniques in Collaborative X-ray Crystallography

On the afternoon of July 10, NIEHS Staff Scientist Lars Pedersen, Ph.D., presented his most recent research results as part of the Laboratory of Structural Biology seminar series. ...[read more](#)



Cell Migration and Metastatic Cancer Cell Behavior

On July 11, visiting lecturer Leslie Rivera Rosado summarized her research data on cell migration mechanisms for an audience of NIEHS scientists. ...[read more](#)



NRDC Climate Center Director Speaks at RTI

Daniel Lashof, Ph.D., director of the Natural Resources Defense Council's (NRDC) Climate Center, was the featured speaker at an Environmental Sciences Climate Change Seminar sponsored by RTI International on July 10. ...[read more](#)



NTP Marks Milestones in Alternatives to Animal Testing

When the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM), convened its annual meeting June 18 – 19 at the Research Triangle Park Radisson Hotel, there seemed to be a general sense of satisfaction about the accomplishments being made... [read more](#)



Upcoming Distinguished Lecturer Alberto Ascherio

The 2007 – 2008 NIEHS Distinguished Lecture Series will welcome its final speaker, Alberto Ascherio, M.D., Dr.P.H., at 11:00 a.m. August 12 in Rodbell Auditorium. ...[read more](#)

NIEHS Spotlight

Special Focus on Superfund



PCBs Are Topic of Superfund Workshop

Just three weeks before the Flood of 2008 engulfed the state of Iowa, 140 scientists from the United States and nine foreign countries convened in

Iowa City, Iowa, to attend the “The Fifth Polychlorinated Biphenyl (PCB) Workshop: New Knowledge from Old Pollutants.” ...[read more](#)

Inside the Institute



NIEHS Takes on the Triangle Triathlon in Style

“I’m retired,” stated trainer and NIEHS scientist Matthew McElwee after finishing the grueling Triangle Triathlon 2008 July 13 at Lake

Crabtree. McElwee is a predoctoral fellow in the NIEHS Comparative Genomics Group. He, along with three of his lab mates, Staff Scientist Elena Braithwaite, Ph.D., Predoctoral Fellow Brooke Tvermoes, and Research Assistant Daniel Snyder, took on the challenge of competing in the event, a USA-sanctioned race featuring a 750-meter swim, 15-mile bike ride and 5K run. ...[read more](#)



Veteran Researcher Colin Chignell Dies Unexpectedly

NIEHS chemist Colin Chignell, Ph.D., died unexpectedly July 16 at age 70 in a drowning accident near North Myrtle Beach, S.C. while on a family vacation.

An NIH employee for 42 years, Chignell was a principal investigator in the Photosensitization Reactions Group in the NIEHS Laboratory of Pharmacology at the time of his death. ...[read more](#)

Extramural Research

Extramural Update

On July 9 in Oakland/Emeryville, Calif., more than 50 representatives from public health and emergency response agencies and occupational safety and health training organizations met to review a draft NIEHS Worker Education and Training Program (WETP) safety and health training tool for earthquake disaster responders. ...[read more](#)

Extramural Papers of the Month

- [Discovery of a Shape-Shifting Protein Could Lead to Anti-Bacterial Agent](#)
- [Maternal Smoking and Receptor Gene Variant Combine to Increase Risk for Childhood Asthma](#)
- [Single Nucleotide Polymorphism is Associated with Neuroblastoma](#)
- [Epigenetic Markers Change Over a Lifetime](#)

Intramural Research

Intramural Papers of the Month

- [The Binding of Cell-Surface Nucleolin and P-selectin Promotes Metastasis](#)
- [NOS and Nitroglycerin-mediated Vasodilation](#)
- [The Involvement of the MEK-MSK1 Pathway in the Immune Response](#)
- [Low Doses of UVA Promote Tumor Growth in Human Keratinocytes](#)

Calendar of Upcoming Events

- **August 5**, in Rodbell Auditorium, 11:00 – 12:00 — Seminar with Ron Crystal, M.D., speaking on “Why Are Some Individuals More Sensitive to the Environment than Others? Genetic Variation and Modulation of Gene Expression in the Human Airway Epithelium”
- **August 5**, in the Executive Conference Room, 12:00 – 1:00 — Seminar, “Antagonism of the Retinoid X Receptor enhances the repopulating capacity of cultured human Hematopoietic Stem Cells,” presented by Rachid Safi, Ph.D.
- **August 6**, in Rodbell Auditorium, 11:00 – 12:00 — Summers of Discovery Seminar Series with Jack Taylor, M.D., Ph.D., talking on “A Random Walk through Biomedical Careers and Gene Polymorphisms”
- **August 12**, in Rodbell Auditorium, 11:00 – 12:00 — Distinguished Lecture Seminar Series featuring Alberto Ascherio, M.D., Dr.P.H., speaking on “Environmental Risk Factors and Biomarkers of Parkinson’s Disease”
- **August 15 (Offsite Event)**, in UNC Bioinformatics Building Auditorium (Room 1131), 10:30 – 11:30 — Joe Piven, M.D. speaking on “Imaging the Developing Brain in Autism” — [Registration Required](#)
- **August 15 (Offsite Event)**, in UNC Molecular Biomolecular Research Building (MBRB) Ground Floor Auditorium (Room G202), 1:00 – 2:00 — Sam Sisodia, Ph.D, discussing “Function and Dysfunction of Presenilins in Alzheimer’s Disease” — [Registration Required](#)
- **August 22**, in Rodbell Auditorium, 9:00 – 10:00 — Frontiers of Environmental Sciences Seminar Series, speaker and topic TBA
- View More Events: [NIEHS Public Calendar](#)

NIEHS Spotlight

Allen Wilcox Honored by University of Bergen

By Eddy Ball

The contributions of NIEHS Senior Investigator [Allen Wilcox, M.D., Ph.D.](#) to the field of epidemiology will be recognized in Norway on August 29, when the University of Bergen will award him an honorary degree. The University's Faculty of Medicine and Dentistry will confer the degree Doctor Honoris Causa during a ceremony to be held in Haakonshallen or "Haakon's Hall," the medieval royal hall of the city of Bergen.

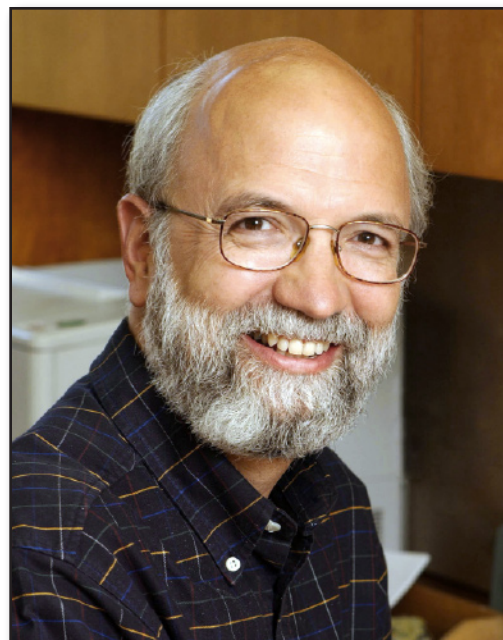
In its notification message, the [University of Bergen](#) commended Wilcox for "major contributions in making epidemiology one of the central disciplines in modern medicine." Wilcox has worked in the NIEHS Epidemiology Branch since 1979 and served as Chief of the Branch from 1991 to 2001. His research has focused mainly on fertility and pregnancy, and he has published more than 150 peer-reviewed articles and more than 50 book chapters, commentaries, editorials and popular-science articles. His book, *Fertility and Pregnancy – An Epidemiologic Perspective*, is scheduled to be published by Oxford University Press in 2009.

Among his contributions to the field is a groundbreaking study on very early pregnancy, in which he and his colleagues established for the first time that one out of four human pregnancies end in very early loss before women even know they are pregnant. His most recent research has focused on birth defects, including [the environmental and genetic causes of cleft lip and palate](#).

Since 2001, he has been Editor-in-Chief of *Epidemiology*, one of the highest-ranked journals in the field of public health. He is past president of the Society for Epidemiologic Research, the Society for Perinatal and Pediatric Epidemiologic Research and the American Epidemiological Society.

The hall where the degree ceremony will be held is part of the Bergenhus Fortress complex in an ancient section of the city known as Holmen. At the time the fortress buildings were constructed, Bergen was the capital of Norway, and Holmen was the main seat of the nation's rulers. Haakonshallen was built around 1260, and one of its first uses was for the wedding and coronation in 1261 of King Magnus Lagabøte. [Haakonshallen](#) remains a major attraction and venue for formal events in the city.

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NIEHS Epidemiologist Allen Wilcox
(Photo courtesy of Steve McCaw)



Haakonshallen, the medieval royal hall where the degree will be conferred (Photo courtesy of Magnus Vabø, University of Bergen)

Looking to the Future of Environmental Public Health

By Eddy Ball

The NIEHS Partnerships for Environmental Public Health (PEPH) working group held its first brainstorming workshop June 30 - July 1 in Rodbell Auditorium. Organized by the program staff in the NIEHS Division of Extramural Research and Training (DERT), the workshop brought together leaders representing diverse groups with a keen interest in environmental public health (EPH) from across the United States in an effort to chart a course for the Institute's continued involvement in EPH over the decade to come.

The PEPH initiative arose from a congressional hearing held in September 2007, when NIEHS Acting Director Sam Wilson, M.D., testified about the Institute's commitment to supporting environmental public health programs and community-based participatory research (CBPR). This testimony led to NIEHS embarking on a series of activities designed to create this new PEPH program. In November 2007, the PEPH working group released a Request for Information (RFI). The RFI elicited some 120 responses about the Institute's role in environmental public health from environmental health researchers, healthcare professionals, educators, policy makers and other members of the public with a vested interest in the effects of environmental exposures on health.

In his welcoming remarks, Wilson reinforced the message he delivered to Congress. "This meeting really is an instrumental opportunity for NIEHS and for the field of environmental health sciences," he said, "to help the Institute frame its approach for moving forward over the next five to ten years. This area represents the research leading edge in real world health implications of environmental exposures — [as well as offering] a way to sharpen our focus on community-based environmental health challenges."

Wilson spoke of the need to determine the "special niche" for NIEHS in the area of environmental public health and "to figure out how we will frame the research program as we go forward."

DERT Susceptibility and Population Health Branch Chief Gwen Collman, Ph.D., filled in the details of the workshop's goals. Collman described the

Brainstorming in Breakout Groups

Throughout the workshop, participants engaged one another, using flip charts to record their ideas on the topic areas:

- Session 1: Partnerships, Tools, Strategies and Resources for Environmental Public Health, moderated by NIEHS Health Science Administrator Christie Drew, Ph.D., of the DERT Program Analysis Branch. This session focused on issues and unmet needs in the areas of building capacity, evaluation, communication and research in the broad field of EPH.
- Session 2: The Unique Role of NIEHS, moderated by Stephani Hines of the University of New Mexico. Participants considered specific ways the Institute can address identified issues and needs noted in Session 1.
- Session 3: Balancing Diversity Needs in Environmental Public Health, moderated by Professor Emeritus Bernie Goldstein, M.D. Participants offered strategies to NIEHS for balancing and prioritizing critical areas and needs.



Seated beside Collman, left, Wilson underscored the need for community-based participatory research (CBPR). "We all know... that many of the situations are local and have to do with ways that certain communities are structured," he said. (Photo courtesy of Steve McCaw)

Institute's need for input from stakeholders about how to create something "unified, integrated and synergistic" to help meet future EPH challenges. She emphasized that the ideas DERT staff had already put forth were "straw men," intended to spark open discussion and a free exchange of ideas. "Everything is a work in progress here," she maintained. "We have no *a priori* ideas about what the workshop product is going to look like."

The workshop was organized around three topics that were designed to start participants thinking broadly and end with more focused recommendations. Each session started with a panel discussion, followed by breakout groups (see text box) and reports back to the full assembly.

As the meeting came to a close on July 1, Collman took a few minutes to reflect on the workshop process and to outline the task ahead for the PEPH working group. According to her, over the next several weeks the group will consider the responses to the RFI, now posted [online](#), along with workshop recommendations to prepare the 10-year plan for the new Partnerships for Environmental Public Health program.

Collman said that she found the workshop process to be very productive. As she hoped, she felt that by the end of the workshop the PEPH team was much closer to the goal of developing a comprehensive ten-year plan. She also thanked the PEPH team for their hard work on this initiative and the workshop planners for developing a strong participatory framework to facilitate exchange of ideas and insights among workshop participants.

In her final remarks, Collman talked about her first fifteen years working in environmental public health and searching for the most effective role for NIEHS. She noted that there have been times when the institute's role and commitment to this area has come into question and said, "In ten years I don't want it to be a question any more."



"What we want to do at this workshop is to work on creating a vision for future programs," Collman told the participants. "This program builds on a lot of investments that we've made over the last decade." (Photo courtesy of Steve McCaw)



According to Collman, the decision to involve NIEHS National Advisory Environmental Health Sciences Council members Hillary Carpenter, Ph.D., shown above, and Stefani Hines as participants was one more indication of the working group's commitment to transparency. (Photo courtesy of Steve McCaw)



Among the leaders in environmental public health attending the workshop was University of Washington Community-Campus Partnerships for Health Program Director Kristine Wong, a seasoned veteran of CBPR on the west coast. (Photo courtesy of Steve McCaw)



Nancy Rothman, Ed.D., director of Community-based Practices at the Temple University School of Nursing, spoke on educational needs for nurses involved in environmental public health. (Photo courtesy of Steve McCaw)



NIEHS Program Analyst Liam O'Fallon, shown during the meeting introduction, played an instrumental role in crafting the November 2007 RFI and analyzing the responses from a diverse mix of stakeholders. (Photo courtesy of Steve McCaw)

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Hrynkow Addresses Embassy Science Officers

By Eddy Ball

NIEHS Associate Director Sharon Hrynkow, Ph.D. gave a talk June 24 on “Perspectives on Global Neuroscience” to members of the Washington Science Diplomats Club meeting at the French Embassy in Washington, D.C.

Hrynkow spoke to an audience of 30 Washington, DC-based foreign embassy science officers representing more than 20 countries. She surveyed recent advances in neuroscience, the linkages between neuroscience and the diplomatic agenda, and emerging social issues that touch on the neurosciences. As one of the Institute’s spokespersons on global health — and a federal liaison to the [Society for Neuroscience International Affairs Committee](#), which co-hosted the event, and the U.S. committee of the [International Brain Research Organization \(IBRO\)](#) — Hrynkow presented a compelling argument for science diplomats to become more aware of neuroscience and mental health as global health priorities.

At the beginning of her talk, Hrynkow discussed the organization and mission of NIH, and its [Blueprint for Neuroscience Research](#) launched in 2004. She noted that nearly half of the 6,000 scientists working at NIH are foreign — many of them specialists in neuroscience — and that international partnerships at the scientist-to-scientist level and at the agency-to-agency level are thriving. Given the setting, she also paid tribute to European icons in neuroscience who “paved the way” for early understanding of the brain and its function — Santiago Ramón y Cajal of Spain, Rita Levi-Montalcini of Italy and Sir John Eccles, an Australian native who received his doctorate at Oxford University in the U.K.

To illustrate the burden of disease of mental illness, Hrynkow drew on the Global Burden of Disease report of the World Health Organization and projections on the global burden of disease in 2020. “By all accounts, non-communicable diseases will contribute increasingly to the global burden of disease in the year 2020,” she noted, “with 70 percent of deaths in developing countries due to non-communicable causes.”

This so-called epidemiologic shift toward non-communicable diseases is based in part on expected strides in addressing the infectious disease agenda, she explained. “Mental illness represents an increasing proportion of the non-communicable burden of disease, with depression as the leading cause of disability in every part of the world, including poorer nations.”

Describing losses to economic output and the rising toll in human suffering, Hrynkow proposed that countries pay increasing attention to issues of mental illness and neuroscience in coming years. However, poorer nations, some of which spend in the order of \$23 per capita per year for health care, will struggle to provide health services for mental illness, and capacity to conduct health research to address local needs is lacking in many countries. Hrynkow pointed to two rays of hope.

First, according to the [Disease Control Priorities Project](#), with existing drugs and with community service, some mental illnesses can be managed even in the poorest of settings. Second, an array of capacity building programs, including those supported by NIH, the IBRO and the [Human Frontier Science Program](#), are making a difference in building much-needed neuroscience capacity in low- and mid-income nations.

Hrynkow addressed a range of social issues about which science diplomats should be aware, with stigma topping the list. “Stigma not only discourages individuals from seeking care,” she noted, “but it also contributes to under-recognition and under-reporting of diseases. In order to make evidence-based decisions on health care policies and programs, it is critical to know the magnitude of the problem, and stigma stymies those efforts.” Hrynkow concluded with her impressions about the stunning advances in neuroscience over the past decades and the need for societies to tackle the tough social and ethical challenges presented by the technical achievements.

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Promoting Hands-on Science in Texas Schools

By Eddy Ball

[NIEHS Grantee](#) Nancy Moreno, Ph.D., delivered an encouraging message to the small, but enthusiastic group of employees and visitors gathered in Rodbell Auditorium on July 2. Her talk on “Environmental Health Partnerships to Improve Science Education” outlined the ways innovation and collaboration have sparked hands-on scientific inquiry across the curriculum in projects in Texas public schools and fostered the involvement of scientists in educating the next generation of citizens. The event was hosted by NIEHS Program Analyst Liam O’Fallon.

Moreno is a professor of Allied Health Sciences and the senior associate director of the [Center for Educational Outreach](#) at the Baylor College of Medicine (BCM). She has been a principal investigator with NIEHS-funded science education programs since they were first funded in 1994. Although the Center now also receives funding from other sources, Moreno credits “the leadership role of NIEHS nationally and within the National Institutes



Hrynkow, shown above at a 2007 lecture, also discussed “neuro-enhancement” and society’s appetite for misusing prescription drugs as neuroscience issues in global health. (Photo courtesy of Steve McCaw)

of Health [for] supporting K-12 science education in very innovative ways and creating an environment in which projects and project staff really can thrive.”

That leadership from NIEHS has encouraged the development of what is now a comprehensive set of programs built upon the long-term partnerships between BCM and schools in the Houston Independent School District. Because recent NIEHS funding for Baylor’s Environment as a Context for Opportunities in Schools (ECOS) project has come in the form of seven-year [Environmental Health Sciences as an Integrative Context for Learning \(EHSIC\)](#) initiative grants, the programs have enjoyed the kind of continuity needed for extensive multi-year evaluation of outcomes.

During her lecture, Moreno described long-term partnerships between BCM and public schools and their shared vision as she presented results of multi-year evaluations of NIEHS-funded programs in public schools in Houston, Texas. Outcomes of the programs’ work with elementary schools included measurements of performance on state examinations, teacher and student content knowledge, science-related language arts and teacher-student interaction.

The BCM team’s comparison of pre- and post-program results showed how effective an integrated, inquiry-based approach to science education can be for students and teachers – even in schools, like Houston’s, that are challenged by economic disparity and high turnover. Hispanic students in particular showed benefits from involvement in the project.

“We have a network of seven magnet high schools, career pathway programs for students and teaching resources,” Moreno explained. “We work with about 200 to 400 teachers a year in professional development, ranging from one-day workshops to programs that last up to two years.” Three of the high schools, she added with pride, are in the top 100 in the United States.

According to Moreno, co-planning and higher education partnerships with K-12 schools benefit everyone from students and teachers to people from every segment of society. These collaborations give students more opportunity and motivation

A Tangible Sign of Success – Buy-in for Baylor College of Medicine’s Programs by the Educational Establishment

In the world of education, pilot programs can come and go, sometimes because they reflect the pedagogical fads of the day that later go out of favor or because they simply are not cost-effective. The BCM Center’s programs, however, have achieved the kind of staying power and establishment buy-in that many programs never enjoy. Two developments in Houston testify to the future of Baylor College of Medicine’s programs:

- District principals put money on the line. Witnessing the benefits of the ECOS project, principals offered to pay for the curriculum in their schools.
- The Houston Independent School District was so impressed with results from the ECOS project and related teacher professional development programs that administrators have offered a contract to Baylor College of Medicine to make BCM the principal elementary science partner for the district.



Speaking of translation, Moreno explained, “We have documented use of the [ECOS] program in more than 30 states. We do work very diligently to disseminate” the program’s resources and best practices. (Photo courtesy of Steve McCaw)

to enter science, technology, engineering and mathematics careers, and they contribute to improved public understanding of the nature of science.

BCM offers an extensive web-based resource center for teachers at a site called [BioEd Online](#). To date, Moreno reported, the web site has had more than 1.2 million visitors who have downloaded more than 10,200 documents in pdf format.

In the future, with the help of an administrative supplement from NIEHS to convert and post all of its materials, BioEd Online will offer even more for teachers everywhere, according to Moreno. It is important to find more ways to share up-to-date science with a larger audience to provide what she called “just-in-time professional development for teachers.” Along with its constantly expanding library of teaching materials, course plans, streaming video and slide sets available free, the site offers virtual workshops, symposia, demonstrations and a teacher certification program.

BCM is currently developing an undergraduate course on genetics and genomics that will be completely free. The course will also be what Moreno described as “asynchronous,” allowing people to participate from anywhere in the world at any time and progress at their own speed.



Moreno acknowledged the role of NIEHS Associate Director Allen Dearry, Ph.D., above, when he oversaw extramural grants during the nascent years of BCM science education programs. (Photo courtesy of Steve McCaw)



Head of the NIEHS Knock Out Mouse Core Manas Ray, Ph.D., left, listened as Moreno described the change in the attitudes of BCM scientists toward science education in the public schools. (Photo courtesy of Steve McCaw)



When Moreno and O'Fallon, shown above, opened the floor for questions, NIEHS Biologist Dori Germolec, Ph.D., prefaced hers with the comment, “It makes me proud that NIEHS is funding this.” (Photo courtesy of Steve McCaw)



NIEHS Epidemiologist Paula Juras, Ph.D., gestured as she suggested that Moreno post her lecture on the web — “so that when I call the science teacher at my daughter’s school, in about ten minutes, I can direct her there.” (Photo courtesy of Steve McCaw)



NIEHS Acting Deputy Director Bill Suk, Ph.D., suggested that sometimes “getting outdoors and getting themselves dirty” can help children develop a passion for scientific discovery. (Photo courtesy of Steve McCaw)

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NIH Continues Search for NIEHS Director

NIH is now accepting applications from qualified candidates for the position of director of NIEHS. The closing date for applications is Monday, August 4, 2008.

Interested individuals may access the position description and instructions for application at <http://www.jobs.nih.gov/vacancies/executive.htm>.

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Superfund Grantee Hammock Honored for Teaching

By Eddy Ball

Veteran Superfund Basic Research Program (SBRP) grantee Bruce Hammock, Ph.D., will receive the 2008 Distinguished Teaching Award for Graduate and Professional Teaching from the University of California Davis (UCD), where he is a distinguished professor of entomology. According to the university, the award, which is sponsored by the UCD Academic Senate, will be presented at an awards dinner in March 2009.

The NIEHS has funded Hammock’s research for more than 30 years. [Hammock](#) has been an SBRP principal investigator since the program started in 1987. He is well respected among colleagues at NIEHS, where he has given several lectures, including an October 2006 talk as part of the NIEHS 2006-2007 Distinguished Lecture Series.

Scores of current and former students supported Hammock’s nomination for the award, as did the chair of his department at the time. The current interim chair of the Department of Entomology, Lynn Kimsey, Ph.D.,

described Hammock as “a campus icon” and “a role model that we should all emulate,” and she praised his commitment to teaching and mentoring. “Despite his international reputation and his many commitments,” she said, “he remains accessible and generously spends hours training and educating students and other professionals.”

Hammock received his bachelor’s degree in entomology from Louisiana State University and a doctoral degree in entomology/toxicology at UC Berkeley. After completing a Rockefeller postdoctoral fellowship at Northwestern University and spending six years at UC Riverside, Hammock joined the UC Davis faculty in 1980.

Hammock holds a joint appointment in Cancer Research with the UC Davis Medical Center. He directs the Superfund Program at UCD, as well as the NIH Training Program in Biotechnology and the NIEHS Combined Analytical Laboratory, where he has performed extensive research into applications of metabolomics methodologies.

With funding from NIEHS Hammock began investigating the role of hydrolytic enzymes involved in the degradation of insect juvenile hormone. These enzymes include esterases and epoxide hydrolases.

His group then looked at the roles of similar enzymes in mammals. As his research progressed, he discovered potential benefits of inhibiting one of them, the soluble epoxide hydrolase, in the treatment of hypertension, pain and inflammation in mammals. In May 2007, Arête Therapeutics, a company he founded, announced that it raised a total of \$51 million to take an inhibitor of the enzyme, a compound know as AR9281, into clinical trials.

The author of more than 650 peer-reviewed articles, Hammock is a leader in his fields of research. He was elected to the National Academy of Sciences in 1999 and has received a long list of awards and recognitions for his achievements. He has received the Frasch and Spencer Awards from the American Chemical Society and the Alexander von Humboldt Award, one of the most prestigious in the field of agriculture. Hammock also received the UC Davis Academic Senate’s Faculty Research Lecturer Award in 2001.

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*Distinguished Teaching Award winner
Bruce Hammock (Photo courtesy of UCD)*

Superfund Puts Trust at the Top in Rhode Island Project

By Eddy Ball

An article published in the July 1 issue of *Environmental Science and Technology* by scientists in the Brown University Superfund Basic Research Program (SBRP) reports on a successful collaboration between a multi-disciplinary research program and community representatives of a contaminated neighborhood in Tiverton, R.I. The report demonstrates the ways that building trust through a multi-stakeholder approach can help residents start to regain the control they feel has been lost because of environmental damage to their communities — and benefit from the scientific research, government programs and community resources that can help them.

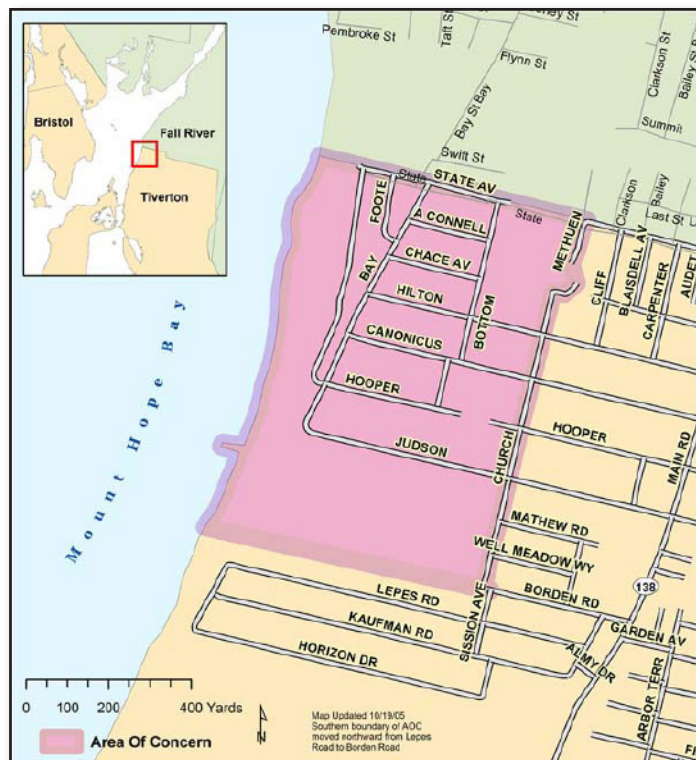
The [article](#) is the latest of 24 publications to emerge from [Reuse In Rhode Island: A State-based Approach to Complex Exposures](#), a four-year SBRP project funded in 2005 by NIEHS. Reuse in Rhode Island has a multifaceted focus, addressing the synergistic toxicity of mixed exposures, developing novel strategies and materials for remediation and mounting a community outreach and empowerment initiative to engage residents in a program to remediate hazardous waste sites in their neighborhoods.

According to the researchers, the outreach core was able to build upon an established long-term relationship with the community-based group [Environmental Neighborhood Awareness Committee of Tiverton \(ENACT\)](#). Tiverton is a town located in the East Bay section of Rhode Island between Aquidneck Island and Fall River, Mass.

Residents of the Bay Street neighborhood of Tiverton were shocked to learn in August 2002 that a municipal crew had discovered soil and sediment contaminated by cyanide, lead, arsenic and other toxicants from a nearby coal gasification plant. Like other residents of contaminated areas, many in the Bay Street neighborhood fell prey to the stress, distrust and frustration that can come with living in a contaminated area where property values suddenly drop dramatically. Because the Bay Street neighborhood was not designated a Superfund site, there was no realistic way for most property owners to recoup their losses.



Brown, shown at the June 30 – July 1 Partnerships for Environmental Public Health Workshop at NIEHS, was corresponding author of the Brown SBRP study. (Photo courtesy of Steve McCaw)



The Rhode Island Department of Environmental Management posted this map of the Bay Street Neighborhood on its [General Summary Web site](#).

According to the researchers, people in this situation come to distrust virtually everyone — government officials, academic researchers and other outsiders. This distrust can be one of the greatest barriers to conducting and translating the kind of research that can lead to remediation and restore lost property value. The Brown team sought to overcome this barrier by partnering with ENACT. In addition to the “professional-to-professional” communication that is a model commonly used by research programs, the SBRP outreach core focused on developing effective ways to facilitate “professional-to-community” communication.

Armed with Brown’s research on mixed exposures, ENACT mounted an aggressive lobbying campaign with the state legislature, culminating in enactment of the Environmentally Compromised Home Opportunity (ECHO) Loan bill in July 2006. ECHO is the brainchild of Professor of Sociology and Environmental Studies Phil Brown, Ph.D., and two of his undergraduate students, and they along with the entire community outreach team, including Laura Senier, first author for the paper, worked to make the aid program a reality. ECHO is an innovative state program that lends up to \$25,000 at relatively low interest rates to residents of areas affected by toxic chemicals and represents a first step toward restoration of the neighborhood.

While the loans have been helpful, for many residents they are still far from adequate. The Brown SBRP team met with state legislators and staff from Rhode Island Housing in the fall of 2007 to craft an agreement to find a way to amend the program, and the scientists continue to collaborate with ENACT to achieve effective cleanup and restoration. The team is also working to disseminate information about their project’s successes to other states where the Rhode Island model of trust building, research translation and outreach could benefit similar communities — as well as to researchers designing any type of research project with an outreach component.

Citation: Senier L, Hudson B, Fort S, Hoover E, Tillson R, Brown P. 2008. Brown Superfund Basic Research Program: A Multistakeholder Partnership Addresses Real-World Problems in Contaminated Communities. *Environ Sci Technol* 42(13):4655–4662. 10.1021/es7023498

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2008 Green Technology Entrepreneurship Academy Meets

By Melissa Fabiano

The University of California Davis (UCD) Center for Entrepreneurship hosted the Green Technology Entrepreneurship Academy (GTEA) 2008 July 7 – 11 in the Tahoe Center for Environmental Sciences at Sierra Nevada College in Incline Village, Nev. This year’s Academy received major funding from the Superfund Basic Research Program (SBRP) and was sponsored by GTEA founding sponsor, the Ewing Marion Kauffman Foundation, along with the Nevada Institute for Renewable Energy Commercialization, the Sierra Angels and the Pacific Gas and Electric Company (PG&E).

According to its organizers, the [2008 Academy](#) broadened its focus on environmental health to include the current state of the global environment and the need to “translate environmentally sustainable technologies and research into viable business ventures.” The Academy’s week-long curriculum was based on the UCD Graduate School of Management’s technology management and entrepreneurship programs.

The week’s agenda featured lectures by academics, entrepreneurs and representatives of non-profit organizations concerned with environmental sustainability:

- Keynote speaker Amory Lovins, co-founder, chairman and chief scientist of the [Rocky Mountain Institute](#)
- UCD Graduate School of Management Professor Andrew Hargadon, Ph.D., director of the [Center for Entrepreneurship](#)
- Bill Moore of Windfarm
- John Hanks of National Instruments
- Scott Lenet of DFJ Frontier
- Susan Mac Cormac of Morrison/Foerster
- Representatives of Ventura Capitalist and the Sierra Angels



Participants of GTEA 2008 gathered for a group photo at the Tahoe Center for Environmental Sciences. (Photo courtesy of the UC Davis Center for Entrepreneurship)

Participants worked in teams to put their new knowledge to use through practical exercises, hands-on experience, teamwork and mentoring sessions.

For five days, 48 participants representing 23 different universities, 17 states and four countries ventured from the safety of their labs into the business world of technology transfer and product commercialization. The Academy's goal in the five-day workshop was to provide these science and engineering doctoral students, post-docs and research faculty with skills to develop, evaluate, translate and market their laboratory research.

Colette F. Quinn, an SBRP graduate student at Dartmouth College, commented on the ways the Academy helped her to re-examine her perspective on scientific research. "Sometimes we, as scientists, get consumed with the fundamentals and perfection," she said, "but in business it is about filling a demand or solving a problem quickly and efficiently." According to Quinn, her experience at the Academy left her more confident about her research, and she determined that she "will market [her] self differently when applying for industrial or consulting positions."

SBRP grantee and Duke University Professor of Molecular Genetics and Microbiology Elwood Linney, Ph.D., agreed. "It was an excellent workshop that was structured well... [and] gave one the organization to recognize what was necessary to bring intellectual property in the form of ideas generated from university research into the commercial field," he said.

From his perspective, Love Sarin, an SBRP graduate student at Brown University, saw the conference as a springboard. "It helped bring home the thought process of figuring out how to think and take action when you have some useful idea[s] with some application in the real world," Sarin explained. "[GTEA] would be a good learning experience for researchers who miss the big picture sometimes."

Attendees interviewed over the past two years have echoed these sentiments and agreed that the GTEA consistently exceeded their expectations. The Academy not only helped scientists develop their ideas, but also, as Sarin commented, "the methodology, the feedback and networks. Everything was useful," he concluded. "These contacts are invaluable."

(Melissa Fabiano is a communications specialist for MDB, Inc., a contractor for SBRP and the Worker Education and Training Program. She is a regular contributor to the *Environmental Factor*.)

Science Camp for Border Students

By Eddy Ball

From the outset, almost everything about the very first University of Arizona (UA) summer camp for the environmental sciences held June 16 – 20 was designed to set it apart from the typical summer camp experience. Created by three Mexican scientists in the UA Superfund Basic Research Program (SBRP), CampCIENCIAS is an innovative program to fill a gap in the summer learning experiences available for high school students living along the U.S.-Mexico border — and make sure that young people had plenty of fun as they explored a variety of science disciplines and unique ecosystems in Arizona.

To be accepted, the twenty students who attended the weeklong overnight camp had to be sufficiently motivated to write an essay about themselves and their hometowns and list the reasons why they were interested in attending the camp.

The camp was free and recruited campers from U.S. towns along the U.S.-Mexico border, including Rio Rico, Yuma, Nogales, Douglas, and the Sonoran Desert settlements of the Tohono O’odham Nation. Another unusual feature of CampCIENCIAS was its ratio of one staff member to every four campers, a degree of personal attention that few educational programs can offer their students.

CampCIENCIAS was the brainchild of three UA SBRP program coordinators — Monica Ramírez, Denise Moreno Ramírez and Rocio Estrella. Having grown up near, along or over the border in Mexico and worked in the SBRP Binational Center, the women understood the needs of the area and shared a commitment to improving science education opportunities for the children there.

When the trio pitched the idea and got the support of the UA SBRP director, Jay Gandolfi, Ph.D., they went to work securing funds for the camp from the UA Technology and Research Initiative Funds, known as TRIF, a state of Arizona tax that funds special investments in higher education.

The campers spent three nights in the Posada San Pedro Hall Dorm on the UA campus and one night at Biosphere 2 in Oracle, Ariz. The days began as early as 5:00 a.m. and included activities on campus and field experiences that kept students busy learning and having fun well into the night.



CampCIENCIAS participants posed for a group shot. Shown in the first row, left to right, are camp leaders and mentors Moreno Ramírez, Jose Luis Camarena, Elaine Situ, Melissa Diaz, Estrella, and Saumya Kumar. (Photo courtesy of Monica Ramírez)



Although the camp's emphasis was science, activities also included border art projects. (Photo courtesy of Monica Ramírez)

Campus activities included visits to the Flandrau Science Center, the UA Museum of Art, the UA Center for Creative Photography, the BIO5 Institute, the UA Laboratory of Tree-Ring Research and the National Optical Astronomy Observatory. Among the places the campers visited off campus were San Pedro Riparian National Conservation Area, Kartchner Caverns, Biosphere 2, Mt. Lemmon and nearby Summer Haven.

By week's end, as graduation ceremonies brought together students, staff and parents, the camp's organizers felt that CampCIENCIAS more than met their expectations. "It's important to provide these types of opportunities to students in order to build their confidence and help recruit a future science work force that can confront environmental and health issues in their own communities," Moreno Ramírez explained.



On one of their many field trips to different ecosystems in Arizona, campers relaxed on a rock outcropping on Mt. Lemmon, AZ. (Photo courtesy of Monica Ramírez)

Estrella expressed her satisfaction that "this weeklong exploratory science expedition opened the possibilities in the minds of these young people," and Ramírez praised "the power of learning experiences outside of the classroom [and] how they improve confidence and motivate science education."

And the kids? Many spoke about learning, and nearly every one of them talked about how much fun they had. "This is the best camp I've ever been to," wrote camper Neal Patel. "I knew this would be fun, but it turned out to be a lot more fun than I ever thought it would be."

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PCBs Are Topic of Superfund Workshop

By Pat Ramstad

Just three weeks before the Flood of 2008 engulfed the state of Iowa, 140 scientists from the United States and nine foreign countries convened in Iowa City, Iowa, to attend the "The Fifth Polychlorinated Biphenyl (PCB) Workshop: New Knowledge from Old Pollutants." Sponsored by the NIEHS Superfund Basic Research Program (SBRP), the workshop was held May 18 - 22, near the campus of the University of Iowa, the event's host and co-sponsor.

Workshop themes reflected the evolution of research interests among scientists concerned with the detection, metabolism, toxicity, remediation and risk assessment of PCBs since they began meeting biennially in 2000. The PCB Workshops alternate between North America and Central and Eastern Europe. Plenary sessions encourage an exchange of information on the latest findings from diverse critical disciplines. Sessions chairs from the University of Iowa, the University of Kentucky, Brown University and University of California, Davis represented four of the NIEHS-funded Superfund Basic Research Programs.

Thomas Sharpe, Ph.D., University of Iowa associate vice president for Economic Development, opened the meeting's Sunday evening reception with welcoming remarks, followed by PCB Workshop host and organizer Professor Larry Robertson, Ph.D., of the University of Iowa. Robertson, who is also director of the Iowa Superfund Basic Research Program (isbrp) acknowledged the support provided by NIEHS and thanked all the sponsors.

Guest lecturer William Suk, Ph.D., NIEHS acting deputy director, spoke on "Strategies for Addressing Environmental Health Needs and Disease Outcomes." Honorary guest Larry Hansen, Ph.D., professor emeritus at the University of Illinois at Urbana-Champaign, provided historical perspective with his lecture on "Forty Years of PCBs — More or Lessons?" Hansen's talk reminded participants of the impact that the simultaneous input from diverse critical disciplines has had on the understanding of PCB health effects over the years. Hansen's presentation also marked a celebration of his retirement.

The three-day program included six half-day sessions, with topics ranging from the analytical "Emissions and Transports of PCBs in Natural and Urban Systems" to policy and regulatory issues, such as one on toxic equivalency factors (TEFs) titled "TEFs: New and Novel Approaches; Implications for Risk Assessment."

Sessions on "Chiral Aspects of PCBs Transport, Metabolism and Distribution" and "New Aspects of Environmental Metabolism of PCBs: From Microbes to Plants to Animals" provided the latest information on environmental, plant and animal metabolism of PCBs.

Mechanistic considerations included a session on the "Reproductive, Developmental and Cardiovascular Effects of PCBs" and the application of those findings to individuals facing real – life exposures in "Anniston: The Most Severe PCB Community Exposure."

As she has for previous PCB Workshops, presenter Linda Birnbaum, Ph.D., of the U.S. Environmental Protection Agency (EPA), contributed a summary presentation at this PCB Workshop. She observed that half of the sessions dealt with environmental sources, fate and transport and transformation.

Birnbaum, who was a scientist at NIEHS from 1980-2001, also noted findings common to previous workshops – that most PCBs ever made are still present in the environment, microbial remediation still needs work, congener information is the key to sources and mechanisms, and lighter congeners are in the air. She then pointed out major differences between this and previous workshops, including decreased emphasis on toxicology except for developmental neurotoxicity, and less focus on endocrine disrupting effects of PCBs.

(Pat Ramstad is program coordinator of the Iowa Superfund Basic Research Program at the University of Iowa.)

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Suk started the SBRP program at NIEHS in 1987. (Photo courtesy of Steve McCaw)



During her summary remarks, Birnbaum told her audience, "Our job as scientists is to look into the future in order to prevent negative health consequences." (Photo courtesy of Steve McCaw)

Science Notebook

Cline Explores Circuits in the Developing Brain

By Robin Arnette

The latest NIEHS distinguished lecture in the 2007–2008 series featured Cold Spring Harbor Laboratory professor Hollis T. Cline, Ph.D., and was hosted by NIEHS Principal Investigator [Serena Dudek, Ph.D.](#) Cline presented “Mechanisms of Circuit Development: The Contribution of Synapse Elimination” on July 8 in Rodbell Auditorium.

Cline is interested in how connections develop within the human brain and how these connections are affected by experience in the relatively simple system present in *Xenopus* (frog) tadpoles. Work from several labs, including Cline’s, have shown that experience affects the frog’s visual system, which consists of the retina, optic nerve and optic tectum (OT), a region of the amphibian brain that is analogous to the superior colliculus in the human brain. Cline explained why this part of the brain was important. “The optic tectum and the superior colliculus are where different sensory modalities converge and regulate motor output. For instance, if you want to kick a soccer ball, you have to see the ball, know where the other players are, and then you can kick it.”

In *Xenopus* the optic nerve is a bundle of axons which sends signals from the retinal ganglion cells to OT cells through connections called synapses. The OT cells process the input and send output to the spinal chord. During frog development, the structure of the ganglion cell axons or axonal projections undergo large-scale arrangement. “The way they do that is by breaking synapses, migrating into a different part of the OT territory and re-establishing new synapses under the guidance of sensory experience,” Cline said.

The axons of retinal ganglion cells, which constitute the pre-synaptic cells in this pathway, aren’t the only ones with the ability to move around in response to visual input. The postsynaptic cells in the OT extend processes toward the axons called dendrites. Cline discovered that dendrites have the same capacity for reorganization. Cline and colleagues used a technique called single cell electroporation to introduce green fluorescent protein (GFP) plasmids into single neurons of a tadpole. The whole organism was placed under a



Cline’s collection of data to document dendritic arbor growth was carefully structured. “We collected time lapse *in vivo* images of these neurons every two hours over a total of six hours and then once a day over a period of several days,” she explained. (Photo courtesy of Steve McCaw)



Visiting Fellow Saverio Gentile, Ph.D., a member of the Membrane Signaling Group, had several questions about Cline’s work. (Photo courtesy of Steve McCaw)

two-photon microscope and a staff member collected a Z-series of time-lapse photos through the neurons of the intact anesthetized animal. The photos revealed that the dendrites, called the dendritic arbor, looked like growing trees with many branches. Images taken at shorter intervals showed that the average lifetime of a branch was only 10 minutes.

Cline hypothesized that visual activity was stabilizing some of the branches so that they could contribute to the growth of the arbor. To test her supposition, she took images of a tadpole with a single tectal cell expressing GFP. She placed the animal in the dark for four hours and took another photo. Then, she placed the animal in a chamber that had light emitting diodes (LEDs) that flashed off and on for four hours. Cline took another micrograph of the tadpole and compared the three photos. She observed that the dendritic arbor experienced an increased growth rate during the period of visual stimulation.

Using electron microscopy, the team reconstructed an entire neuron and mapped the location of every synapse. The micrographs indicated that a branch could be extended, retracted or stable depending on the amount of synapses. “Branches that are actively extending have the highest synapse density, while those that are retracting have relatively few synapses,” Cline stated. This means that many extra synapses are made on extending branches and they are retracted as the branches stabilize.

Cline’s work has shown that axons and dendrites use different synapse formation strategies when switching between extending and stable branches. Axons initiate new contacts with postsynaptic partners by sharing pre-existing synaptic contacts; dendrites add new branches, which are the primary site of synaptogenesis. Diseases or agents which affect branch addition, synapse formation or synapse elimination will affect circuit development and brain function.

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Receptor Biology Group Research Fellow Yukitomo Arao, Ph.D., pondered Cline’s demonstration of the effects of environmental factors on nervous system development. (Photo courtesy of Steve McCaw)



Similarly, Gene Regulation Biologist Yin Li, Ph.D., looked intrigued during Cline’s detailed account of the way the dendritic arbor reacts to stimulus. (Photo courtesy of Steve McCaw)

Laboratory of Structural Biology Undergoes Scientific Review

By Robin Arnette

Every four years laboratories at NIEHS meet with their Board of Scientific Counselors (BSC) to ensure that the labs are carrying out sound hypothesis-based research. On July 21–22 in Rodbell Auditorium, the [Laboratory of Structural Biology \(LSB\)](#) underwent its review to provide a thorough examination of the lab's studies, programs and core facilities.

This year's LSB BSC Review Board was comprised of 12 members, 10 scientists from outside institutions and two from NIEHS, Acting Scientific Director Perry Blackshear, M.D., D.Phil., and Deputy Scientific Director Steven Akiyama, Ph.D. Chairing the Board was [Steven Belinsky, Ph.D.](#), head of the Lung Cancer Program at the Lovelace Respiratory Research Institute in Albuquerque, NM. Board members and an audience made up of NIEHS scientists were treated to talks by LSB researchers during morning and afternoon sessions. The afternoon poster session was also open to the public.

Prior to the presentations, NIEHS Acting Director Samuel Wilson, M.D. gave a brief welcome address and thanked BSC members on behalf of the institute. "I can't say enough to express our appreciation for your taking time to participate in this incredibly important peer-review activity," he said. LSB Lab Chief Thomas Kunkel, Ph.D., followed Wilson with an overview of ongoing projects.

The mission of LSB is to provide insight into biological processes that modulate the effects of environmental exposures on human health. To accomplish this goal, the lab combines biochemical and genetic approaches with X-ray crystallography, nuclear magnetic resonance (NMR), mass spectrometry and computational chemistry to investigate the structures of macromolecules at the atomic level.

Robert London, Ph.D., head of the Nuclear Magnetic Resonance (NMR) Group, gave the first presentation and talked about his group's interest in enzymes involved in DNA replication or repair and ligand-macromolecule interactions. He said, "An understanding of these DNA replication and repair mechanisms provides insight into how damage produced by physical or chemical agents is dealt with in humans and other living systems."



Laboratory of Structural Biology Chief Thomas Kunkel (Photo courtesy of Steve McCaw)



Board Chair Belinsky, center, and Akiyama, right, enjoyed one of the lighter moments of the presentations. (Photo courtesy of Steve McCaw)

The Mass Spectrometry Group, led by Kenneth Tomer, Ph.D., studies biomolecules related to immunological or inflammatory response to exposures and biomolecules damaged by environmental exposures or those involved in their repair. He believes that his work will lead to a better understanding of the biological responses initiated by environmental exposures and possibly how to prevent the damage.

The study of the structure and function of macromolecules involved in post-transcriptional gene regulation is the aim of the Macromolecular Structure Group, directed by Traci M.T. Hall, Ph.D. Hall said that although the general public may have a hard time understanding the research, the group's experiments "will lead to an appreciation for how these gene regulatory pathways are important in human biology and diseases."

The Computational Chemistry & Molecular Modeling Group, led by Thomas Darden, Ph.D., develops tools that aid in the understanding of structural, mutational and sequence data. Scientists use these tools to help other NIEHS investigators in their scientific endeavors.

In addition to their work as a whole, LSB is proud of its training programs, in particular the Second Mentor Program, which allows LSB fellows to name an additional principal investigator who can provide advice on all areas of professional development as well as impart scientific guidance.

The Board had several closed sessions following the open session and adjourned the meeting the next day. Belinsky said he was pleased to have chaired the review and placed the Board's purpose into context. "Providing feedback is a very important component of the NIEHS because it helps the investigators maintain an excellent level of research," he explained. "It really preserves the future of environmental health science."

Kunkel concurred and spoke on behalf of LSB. "Thoughtful peer-review is critical to success in science, and for this reason, all members of LSB are very grateful to members of the BSC for their time, careful deliberations and advice," he said. "I also want to thank Perry Blackshear and Steve Akiyama for their time and efforts."

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Tomer, shown above, left the podium as he described the accomplishments of the Mass Spectrometry Group. (Photo courtesy of Steve McCaw)



BSC member and York University Department of Chemistry Research Chair Michael Siu, Ph.D., center; and Kunkel, right with yellow tie, listened intently as LSB group heads explained their work. Shown to the left of Siu is LSB NMR contractor Eugene DeRose, Ph.D. (Photo courtesy of Steve McCaw)



Board member Joann Sweasy, Ph.D., center; who presented a Genetics Training Action Committee invited lecture at NIEHS in April, found herself on the other side of the podium during the review. (Photo courtesy of Steve McCaw)

Epigenetic Changes May Be Early Indicators of Cancer

By Dixie-Ann Sawin

A recent NIEHS-funded study headed by Stephen B. Baylin, M.D., at The Johns Hopkins Kimmel Cancer Center in Baltimore, Md., adds to the evidence that mutation and epigenetic phenomena in common genes may be early prognosticators of cancer. This study, published in *PLoS Medicine*, has important implications that may improve early detection or impact treatment outcomes.

The authors of the [study](#) state that it is very unlikely for a given gene in breast and/or colon cancer to have mutations, hypermethylation and reduced expression and be localized to cancer mutation “hotspots” without also being important for tumor development. Working with this hypothesis, the researchers used an initial microarray strategy to screen a large pool of genes that bear low incidence heterozygous missense mutations for hypermethylation and expression status. Their aim was to identify genes that may have potential prognostic value.

The researchers used an unbiased genome-wide microarray approach to analyze potential gene targets of mutation and hypermethylation in breast and colon cancer cell lines and tumor tissue. Hypermethylation of CpG islands is an epigenetic silencing mechanism that is prevalent in cancer progression.

The team found that 56 out of 189 were potential candidate hypermethylated genes. Of these 56, they determined that 36 were in fact hypermethylated. They further determined that half of these were methylated in cell lines only and the other 18 were methylated in primary tumor tissue but not normal tissue.

Of particular note, the researchers observed that genes mutated in colon cancer, but not in breast cancer, may be hypermethylated in breast cancer and not in colon cancer. They also found that mutation and methylation were not always mutually exclusive.

Using Gene Ontology classification, the team determined that a number of the 18 hypermethylated genes were involved in signal transduction, cell adhesion and motility. Six were potential tumor suppressor genes. Sixteen of these 18 genes mapped to loci that were deleted in various cancers.

With regard to diagnosis of cancer, tumor stage and grade are among the strongest indicators of survival and propensity for metastasis in breast and colon cancer. Thus, the researchers sought to determine whether the expression of these genes could correlate to any of those indicators.

What they found was intriguing. Decreased expression levels of seven genes were associated with “unfavorable clinical characteristics in breast, colon cancer, or both.” Decreased expression of five of these genes was associated with decreased survival, and four genes showed decreased expression with increasing tumor grade.

The researchers acknowledged that there are limitations to their study in that they did not address the biological effects of the individual mutations and that their data uses only 13,023 previously sequenced genes. More have recently been identified.



Baylin, above, talked on “Cancer: The Environment and the Epigenetic Interface” during his February 2007 Distinguished Lecture at NIEHS. (Photo courtesy of Steve McCaw)

Their results suggest that mutation and epigenetic events both contribute to breast and colon cancer development. Their study advances the large-scale analysis of genetic and epigenetic phenomena in the discovery of potential cancer candidate genes.

Citation: Chan TA, Glockner S, Yi JM, Chen W, Van Neste L, Cope L, Herman JG, Velculescu V, Schuebel KE, Ahuja N, Baylin SB. 2008. Convergence of mutation and epigenetic alterations identifies common genes in cancer that predict for poor prognosis. *PLoS Med* 5(5):e114.

(Dixie-Ann Sawin, Ph.D., is a post-doctoral research fellow in the Laboratory of Neurobiology/Neurotoxicology Group.)

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Team Develops Novel Method to Monitor DNA Damage Recognition

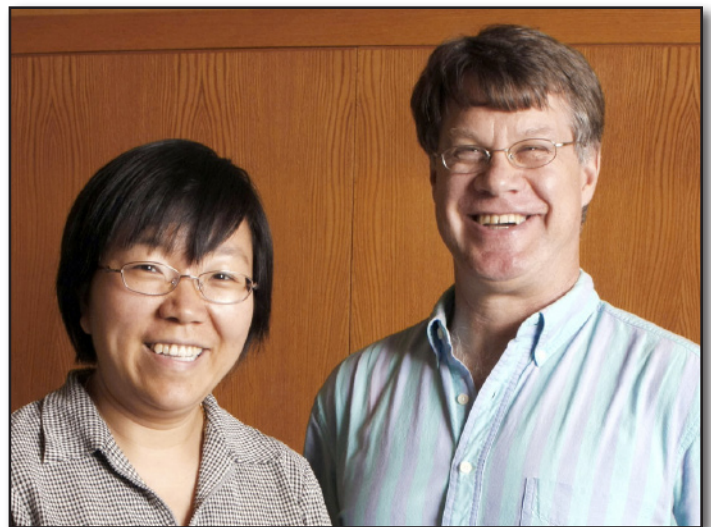
By *Senyene Hunter*

In a study published in the June issue of *Nanoletters*, Principal Investigator Bennett Van Houten, Ph.D., and Postdoctoral Fellow Hong Wang, Ph.D., in the NIEHS Laboratory of Molecular Genetics [DNA Repair and Mitochondrial Damage Group](#), along with their collaborators from the University of North Carolina, present novel methods that overcome obstacles encountered in single-molecule studies. The method involves the application of nanotechnology using quantum dots to characterize proteins.

Quantum dots are nanometer scaled fluorescent probes that have the advantage of being highly photostable, while displaying strong emission intensities. Using nanoparticles such as quantum dots to label and monitor the behavior of individual proteins is a relatively new development that could greatly advance biochemical research, particularly

in the area of protein-DNA interactions. However, certain challenges have thus far restricted the use and effectiveness of these techniques. In the past, the use of quantum dot-conjugated proteins was limited by the inability to reliably determine the number of proteins attached to each quantum dot and the retained functionality of the conjugated proteins.

To overcome this problem, [Wang and colleagues](#) attached quantum dots to the protein UvrB using an antibody-sandwich method. UvrB is a bacterial DNA damage recognition protein involved in nucleotide excision repair. In this method, an epitope tag was attached to UvrB and antibodies were used as “adaptors” to connect the quantum dot to the tagged UvrB protein. Wang and colleagues then used atomic force microscopy (AFM) imaging to demonstrate the successful conjugation of a single quantum dot to one UvrB molecule, conclusively demonstrating a 1:1 stoichiometry. As Wang explained, AFM is a tool used for studying single molecule biomolecular interactions that “works in the same way as our fingers, which can touch and probe the environment. The ‘finger’ in AFM is a sharp tip which has a radius at nanometer scale.”



Wang, left, and Van Houten had reason to celebrate their new method for monitoring DNA repair molecule by molecule. (Photo courtesy of Steve McCaw)

The researchers also used AFM to identify interactions between quantum dot-conjugated UvrB (UvrB-QD) and its binding partner UvrA. These analyses indicated that UvrB-QD was still functional and that the presence of the quantum dot did not disrupt protein-protein interactions. The team was also able to use AFM imaging to visualize UvrB-QD conjugate loaded on to a DNA substrate containing damage by UvrA.

To verify results obtained via AFM imaging, Wang employed an agarose gel-based electrophoresis mobility shift assay (EMSA). EMSA is a commonly used and widely accepted method of evaluating the nucleic acid binding function of a protein. The investigators used EMSA analysis to demonstrate that “the UvrB-QD conjugate remains functional for DNA damage recognition and can be loaded specifically onto damaged DNA by UvrA.”

Findings discussed in the paper have a wide range of applications. “These methods can be applied to any protein that has an epitope tag. In addition, these advancements will help further the use of quantum dot-labeled proteins in living cells to study intracellular processes,” said Wang. Van Houten added, “Our long term goal is to use epi-fluorescence microscopy to follow these proteins in real time as they ‘walk along’ DNA in search of DNA damage. Ultimately we want to be able to visualize DNA repair, molecule by molecule, as they assemble on the site of damage and remove the DNA adduct.”

Citation: Wang H, Tessmer I, Croteau DL, Erie DA, Van Houten B. 2008. Functional characterization and atomic force microscopy of a DNA repair protein conjugated to a quantum dot. *Nano Lett* 8(6):1631-1637.

(Senyene Hunter, Ph.D., is a postdoctoral fellow in the NIEHS DNA Repair and Mitochondrial Damage Group.)

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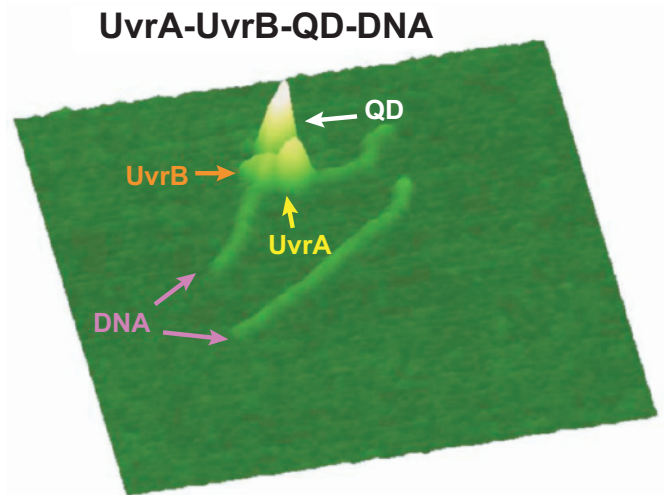
New Techniques in Collaborative X-ray Crystallography

By *Andrea Moon*

On the afternoon of July 10, NIEHS Staff Scientist Lars Pedersen, Ph.D., presented his most recent research results as part of the Laboratory of Structural Biology seminar series. Pedersen heads the NIEHS [Structure & Function Group](#), also known as the Collaborative Crystallography Group, which exists to aid intramural scientists in structural determination for proteins of current research interest.

In a talk titled “You Don’t Always Have to Punt on 4th and Long: Crystal Structures of RACK1A from *Arabidopsis thaliana* and a Heparan Sulfate (HS) Sulfotransferase from Chicken,” Pedersen shared some of the challenges he has encountered collaborating with scientists in other groups to express, purify and solve the structure of a protein.

The metaphor in Pedersen’s title refers to those desperate moments in American football — fourth down and much more than ten yards to go — when getting that elusive first down seems impossible. In these kinds of



Researchers used AFM imaging to observe the UvrB-QD conjugate complexed with UvrA and specifically bound to a damaged site in a DNA fragment. (Image courtesy of the NIEHS DNA Repair and Mitochondrial Damage Group)

situations, Pedersen's group has implemented a new "trick play" to obtain that far off first down. Two recent accomplishments of this kind include co-authorship on studies pertaining to signal transduction with members of the Laboratory of Neurobiology and [heparan sulfate biosynthesis](#) with investigators at the University of North Carolina at Chapel Hill (UNC-CH).

Structural biologists have long used x-ray crystallography as a tool for studying protein structure. The technique allows scientists to obtain atomic resolution three-dimensional "pictures" of the protein structure. According to Pedersen, since structure dictates function throughout nature, determining the structure of a protein opens the door to a better understanding of how it works.

To illustrate the importance of employing new ideas and techniques in X-ray crystallography to overcome problematic projects, Pedersen described a successful collaboration with Jian Liu, Ph.D., at the UNC-CH Eshelman School of Pharmacy.

After unsuccessfully attempting to express and crystallize a heparan sulfate (HS) sulfotransferase from hamster, Pedersen and his colleagues decided to switch species and use chicken instead. Because chickens have a higher body temperature than humans, their proteins are thought to be more thermostable than human proteins. When the chicken protein still refused to crystallize, the team used a fusion protein system that employed the maltose binding protein (MBP). The fusion protein was much more stable and yielded crystals which diffracted to 2.65Å, a measure that is close to the 1.5 Å distance between two covalently bonded atoms.

Another "stubborn" project that Pedersen had to contend with involved the protein RACK1A, a signal transduction protein that has a similar structure to that of the G_{β} protein, but lacks a similar function. The project was done in collaboration with David Armstrong, Ph.D., head of the Membrane Signaling Group at NIEHS. After attempting to crystallize RACK1A in its native form from the plant *A. thaliana*, Pedersen made an MBP-fusion construct. In this case, merely using the fusion system was not enough. Pedersen and team members also needed to alter the ability of the fusion protein to crystallize by making mutations of surface residues. The resulting crystals diffracted to 2.4Å and produced solid data.

Obtaining the crystal structure of RACK1A and the HS sulfotransferase proteins has allowed for a greater understanding of their function.

(Andrea Moon is a biologist in the NIEHS Collaborative X-ray Crystallography Group, a part of the Laboratory of Structural Biology)

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*Collaborative Crystallography Group Leader
Lars Pedersen (Photo courtesy of Steve McCaw)*

Cell Migration and Metastatic Cancer Cell Behavior

By Dixie-Ann Sawin

On July 11, visiting lecturer Leslie Rivera Rosado summarized her research data on cell migration mechanisms for an audience of NIEHS scientists. Her seminar, “Role of $\alpha4\beta1$ -Integrin in Cell Migration,” was hosted by Steven Akiyama, Ph.D., lead investigator of the Cell Adhesion group within the Laboratory of Molecular Carcinogenesis.

Rivera is a seventh-year biochemistry, cellular and molecular biology graduate student in the lab of Joy Yang, Ph.D., at Johns Hopkins University in Baltimore, Maryland. The primary aim of her work in the [Yang lab](#) is to elucidate regulatory mechanisms involved in cell migration with the hope of increasing the understanding of roles played by integrin-mediated molecular interactions in cancer.

Rivera’s talk focused on alpha4beta1 ($\alpha4\beta1$)-integrin, a unique member of the integrin superfamily that is involved in regulating directional cell migration. This integrin belongs to a subgroup that not only mediates extracellular matrix adhesion, but can also play roles in cell-cell adhesion in placental and cardiac development as well as tumor angiogenesis. As Rivera explained, her interest in this field stems from the relevance of such migratory mechanisms to metastatic tumor cell progression.

Rivera presented results of her [recently published work](#), for which she was a co-first author. In the study, she used the Shear Flow Assay to examine the role of $\alpha4\beta1$ -integrin in cell migration in Chinese Hamster Ovary (CHO) cells. Fluid shear stress is associated with changes in blood flow which can impact angiogenesis and tumor development. Using this model, she questioned whether molecular interactions between $\alpha4\beta1$ -integrin and paxillin, the signaling adaptor protein, influenced cell migration.

In her study, she ectopically expressed wild type and mutant forms of $\alpha4\beta1$ -integrin in CHO cells and observed that $\alpha4\beta1$ -integrin promotes directional cell motility — a mechanism that involves formation of membrane protrusions, known as lamellipodia, at the leading edge of cells and retraction at the trailing edges. In her presentation, Rosado showed short videos that clearly demonstrated migratory differences between wild type and mutant CHO cells.

The model underscored the importance of molecular interactions between the only known phosphorylation site (Ser988) on the $\alpha4$ integrin subunit and the paxillin-binding site (Y991A) in mediating cell polarity and migration of cells. Rivera showed that disrupting both phosphorylation and paxillin sites led to unstable cell polarization and that these interactions may have an effect on Rac and Rho GTPase-mediated pathways. She also determined that $\alpha4\beta1$ -integrin can associate with the non-muscle myosin heavy chain IIA protein and that this association also plays an important role in regulating cell migration. Her work provides novel insight into the role played by integrins in cell migration and metastatic tumor cell growth.

(Dixie-Ann Sawin, Ph.D., is a post-doctoral research fellow in the Laboratory of Neurobiology/Neurotoxicology Group.)



Guest lecturer Leslie Rivera Rosado
(Photo courtesy of Leslie Rivera Rosado)

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NRDC Climate Center Director Speaks at RTI

By Eddy Ball

Daniel Lashof, Ph.D., director of the Natural Resources Defense Council's (NRDC) Climate Center, was the featured speaker at an Environmental Sciences Climate Change Seminar sponsored by RTI International on July 10. Lashof spoke to an audience of people from RTI, the Environmental Protection Agency (EPA) and NIEHS, where researchers are particularly interested in the health effects of climate change. RTI Senior Fellow R.K.M. Jayanty, Ph.D., was the host for the seminar, which was held in an auditorium adjacent to the RTI campus in Research Triangle Park.

Among its many advocacy activities, the NRDC performs or commissions analyses of proposed legislation to reduce emissions of heat-trapping pollutants. In his talk, "Renewable Energy and Economic Impact," Lashof reported on an assessment of the Lieberman-Warner Climate Security Act (S. 3036) substitute amendment. The assessment was conducted at the request of the NRDC by the International Resources Group (IRG). The Senate Environment and Public Works Committee sent this bill to the full Senate for consideration on May 21.

Lashof noted that the legislation and its associated costs, projected through 2050, were hotly debated on the Senate floor and in the media. Although the amendment had the support of a majority, a vote on June 6 to invoke cloture to halt debate failed to muster the necessary 60 votes, effectively killing the amendment for the 2008 term.

Despite the defeat of the amendment, Lashof said, "it certainly focused the attention of the Senate on climate in a way that had never happened before." He predicted that the amendment or something similar will be introduced again in 2009 and likely will pass, especially since both presidential candidates have expressed support for limiting emissions.

According to Lashof, the IRG analysis concluded that the economic impact of the Lieberman-Warner amendment provisions for setting a cap on U.S. emissions of greenhouse gases would actually be small compared to business as usual. The analysis was performed using a version of the U.S. national MARKAL model (US-NM50) originally developed by the Environmental Protection Agency's Office of Research and Development. It found that the cost of increased investment in more efficient appliances,



Lashof, above, specializes in national energy policy and has testified on aspects of global warming and energy policy before several congressional committees. (Photo courtesy of Steve McCaw)



Lecture host Jayanty said that he was gratified to see visitors from NIEHS and EPA at the event. (Photo courtesy of Steve McCaw)

equipment and low-carbon technologies would be in large part offset by savings from reductions in use of carbon-producing fuels.

The key features of the proposed legislation included dramatic reductions in emissions:

- Starting from 2005 levels, the bill progressively would cut emissions of carbon dioxide and four other global warming pollutants by 4 percent in 2012 to 71 percent in 2050.
- Emissions of heat-trapping hydrofluorocarbons (HFCs) would be cut more rapidly, declining from 2012 levels by at least 15 percent in 2020 to 70 percent by 2040.
- Additional emission reductions would be achieved outside the cap by dedicating more than five percent of the emissions allowances to reducing emissions in the domestic agriculture and forestry sectors and to international efforts to reduce deforestation and increase technology cooperation.

“Most of the reductions come from the electric sector,” Lashof explained. “We also have some modest reductions in transportation.... We find a big contribution from renewable energy [such as wind, photovoltaic and concentrating solar power].... There is also a substantial reduction in conventional coal, mostly after 2030.”

Interestingly, the IRG analysis did not find the “rush to natural gas” that some critics have predicted as a consequence of reducing emissions. Lashof also pointed to the potential of using carbon captured from coal to enhance oil recovery from existing fields, which he said may yield as many as 50 billion barrels of oil that are too expensive to recover currently and may ease the transition to alternative sources of energy for transportation.

Lashof said he is encouraged that the conversation about greenhouse gases has shifted from questions of whether climate change is actually a reality to questions about the best ways to go about addressing it. He is hopeful that legislation and incentives will encourage market forces to put more affordable alternatives in place sooner rather than later.

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NIEHS Bioethicist David Resnik, J.D., Ph.D., was curious about the population growth assumptions in the NRDC analysis, noting that declines in growth, such as those several European countries are now experiencing, could impact what actually occurs by 2050. (Photo courtesy of Steve McCaw)



The lecture was an informal event, with many attendees having lunch during the talk. (Photo courtesy of Steve McCaw)

NTP Marks Milestones in Alternatives to Animal Testing

By Eddy Ball and Robin Mackar

When the [Scientific Advisory Committee on Alternative Toxicological Methods \(SACATM\)](#), convened its annual meeting June 18 – 19 at the Research Triangle Park Radisson Hotel, there seemed to be a general sense of satisfaction about the accomplishments being made by the [Interagency Coordinating Committee on the Validation of Alternative Methods \(ICCVAM\)](#) and the [NTP Interagency Center for the Evaluation of Alternative Toxicological Methods \(NICEATM\)](#). The meeting provided an opportunity for federal agencies to discuss the progress each was making in implementing the NICEATM-ICCVAM Five-Year Plan, celebrate accomplishments, enjoy some lively debate and discuss future directions.

After some brief welcoming and introductory remarks by ICCVAM Chair Marilyn Wind, Ph.D., and NTP Associate Director John Bucher, Ph.D., on behalf of NTP Acting Director Samuel Wilson, M.D., the meeting was turned over to the SACATM Chair, James Freeman, Ph.D.

The meeting commenced with two presentations, one by NTP scientist Bill Stokes, D.V.M., the executive director of ICCVAM and director of NICEATM, and one by Kim Boekelheide, Ph.D., of Brown University.

Stokes opened with a progress report on ICCVAM and NICEATM activities during the past year including the tenth anniversary celebration of ICCVAM in February, which coincided with release of the committee's [Five-Year Plan](#). The plan outlines strategies for researching, developing, translating, validating and promoting new and revised non-animal and other alternative assays for integration of the three Rs — reduction, refinement, and replacement of animal testing— into Federal agency testing programs through 2012.

As ICCVAM looks forward, Stokes said, the committee also reflected on accomplishments over the past decade. “Seventeen alternative methods have been accepted or endorsed by US federal agencies since 1999... [and] include alternative methods that can be used to reduce and refine animal use for the most commonly conducted product safety tests,” he explained. “Twelve of these are non-animal methods, [and] ten of those seventeen are based on ICCVAM technical evaluations and recommendations.”



Freeman, center; monitored discussion by SACATM members. Seated behind him and to the right is Bucher. (Photo courtesy of Steve McCaw)



The meeting was the first for NTP Executive Secretary Lori D. White, Ph.D., left, and NIH Deputy Director for Extramural Research, Norka Ruiz Bravo. (Photo courtesy of Steve McCaw)

Stokes then discussed the recent [approval](#) of two new alternative methods recommended by ICCVAM to reduce live animal use for ocular safety testing. The two alternative test methods, the bovine corneal opacity and permeability (BCOP) assay and the isolated chicken eye (ICE) assay, are the first scientifically valid alternative methods to gain regulatory acceptance for ocular safety testing.

Stokes also emphasized that increasing international cooperation will be instrumental in helping the testing community adopt more alternative methods over the next five years. Stokes was pleased to acknowledge that a representative of the European Centre for Validation of Alternative Methods (ECVAM) and the director of the Japanese Center for Validation of Alternative Methods (JaCVAM) were attending the meeting, and noted the increasing collaborations among the three organizations, as well as ICCVAM participation in several international forums.

Boekelheide finished out the morning with a summary of the National Research Council report, *Toxicity Testing in the 21st Century*. He discussed why the NRC panel was established, the Panel's charge and its recommendations, as well as some of his own personal views on the need for a paradigm shift for toxicity testing.

“This is not something that anyone expects to happen overnight,” Boekelheide said of the implementation. “The Panel was thinking in the 20- to 50-year time frame for this to come about.”

He pointed out that one of the most attractive features of the report is its focus on mechanisms of action and toxicity pathways rather than phenotypic responses. “It's the new science, and I think that's an important driver.”

The afternoon sessions focused on short individual presentations by agency representatives on the role they are playing related to the implementation of the Five-Year Plan.

“A Very Loaded Mission Statement”

In her opening remarks, Marilyn Wind, Ph.D., chair of ICCVAM and principal ICCVAM representative for the Consumer Product Safety Commission, talked about the importance of the role of SACATM, anchoring her comments with the ICCVAM mission statement:

The ICCVAM mission is to facilitate the development, validation and regulatory acceptance of new and revised regulatory test methods that reduce, refine and replace the use of animals in testing, while maintaining and promoting scientific quality and the protection of human health, animal health and the environment.

The mission statement, Wind went on to explain, is “loaded” both because its goals are noble, but difficult to achieve, and because of ICCVAM's role as a facilitator, rather than a test method developer or regulatory agency. ICCVAM can encourage others who have the resources to put forth methods for validation — and give developers guidance during the process — but the ultimate acceptance of methods by regulatory agencies depends on successful completion of a scientifically rigorous process.

The bottom line, Wind reminded SACATM members, is that “we need to do all this while still maintaining, if not improving, the safety in terms of humans, the environment and animals. The role that you play in giving us feedback and helping us maintain good science at the same time that we are encouraging and facilitating the three R's is extremely important.”

In recognition of their work on the NICEATM-ICCVAM Five-Year Plan, Wind and eleven other members received an NIH Director's Group Award on July 21:

NIEHS — William Stokes, D.V.M., Sheila Newton, Ph.D., Deborah McCarley, Raymond Tice, Ph.D.

Other ICCVAM Agency Representatives— Suzanne Fitzpatrick, Ph.D., FDA; David Hattan, Ph.D., FDA; Abigail Jacobs, Ph.D., FDA; Jodie Kulpa-Eddy, D.V.M., USDA; Alan Poland, M.D., NCI; Amy Rispin, Ph.D., EPA; Margaret Snyder, Ph.D., NIH, Office of the Director

Attending her first meeting of SACATM, Norka Ruiz Bravo, Ph.D., NIH deputy director for Extramural Research, highlighted some of the scientific projects NIH is supporting in relation to the NICEATM-ICCVAM Five-Year Plan, including the development of non-mammalian models such as zebra fish. Bravo also talked about the significance of the Memorandum of Understanding signed between NIH and EPA to screen chemicals more rapidly, the value of microarray gene chips in research efforts and the advantages of 3-D tissue models to help accelerate discovery and safety evaluations of therapeutic agents.

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



Wind, left, and Stokes listened to SACATM comments on their reports about ICCVAM milestones and plans to expand available alternative tests in the next five years. (Photo courtesy of Steve McCaw)



ICCVAM Vice-Chair Jodie Kulpa-Eddy, D.V.M., of the Department of Agriculture, center, responded to the one public comment on the ICCVAM report. She is shown with Department of Defense representative Peter Schultheiss, D.V.M., Col. US Army, left, and ECVAM representative Jens Linge, Ph.D., right. (Photo courtesy of Steve McCaw)

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Upcoming Distinguished Lecturer Alberto Ascherio

By Eddy Ball

The 2007 – 2008 NIEHS Distinguished Lecture Series will welcome its final speaker, Alberto Ascherio, M.D., Dr.P.H., at 11:00 a.m. August 12 in Rodbell Auditorium. Ascherio will explore the topic of “Environmental Risk Factors and Biomarkers of Parkinson’s Disease.” The lecture will be hosted by [Honglei Chen](#), M.D., Ph.D., a tenure-track investigator in the Aging and Neuroepidemiology Group.

[Ascherio’s research](#) is primarily devoted to finding the causes of multiple sclerosis (MS), Parkinson’s disease and amyotrophic lateral sclerosis. For more than a decade, he has investigated neurodegenerative diseases in several large cohorts comprising more than 400,000 men and women who have provided detailed information on their dietary habits and lifestyle, in addition to blood or cheek cell samples for genetic and other laboratory analyses.

Currently, Ascherio directs a large prospective sero-epidemiological study based on the Department of Defense Serum Repository to identify prediagnostic markers of infection and nutritional status in relation to MS risk and collaborates with the Parkinson Study Group to investigate risk factors for Parkinson’s disease progression.

A native of Italy, Ascherio trained in internal medicine in Italy, and from 1980 to 1988 he practiced medicine and public health in Latin America and Africa. He came to the United States in 1988 and earned a doctoral degree in epidemiology from the Harvard University School of Public Health in 1992.

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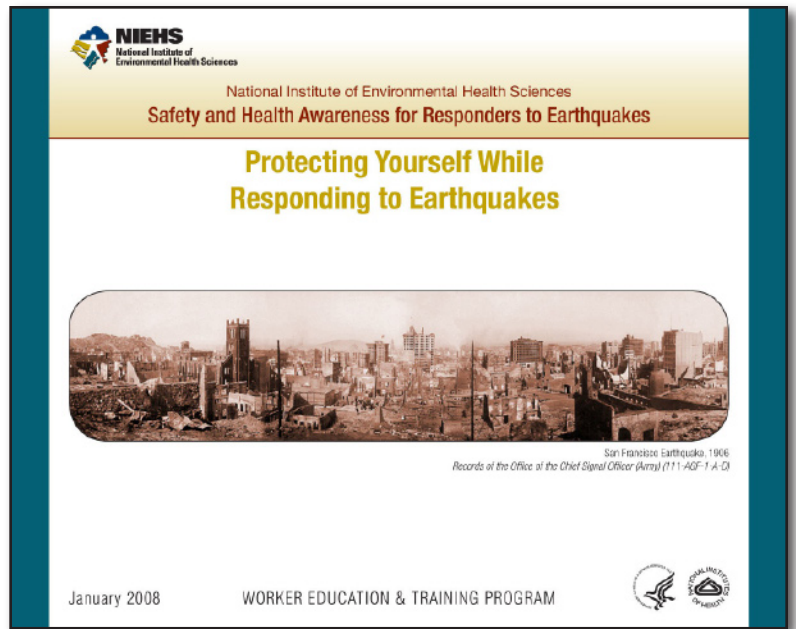


Distinguished Lecturer Alberto Ascherio (Photo courtesy of Leslie Unger and Harvard University)

Extramural Update

Stakeholders Review Draft on Earthquake Responder Training

On July 9 in Oakland/Emeryville, Calif., more than 50 representatives from public health and emergency response agencies and occupational safety and health training organizations met to review a draft NIEHS Worker Education and Training Program (WETP) safety and health training tool for earthquake disaster responders. The program was titled “Safety and Health Awareness for Responders to Earthquakes,” and attendees included staff from the NIEHS WETP and the National Clearinghouse for Worker Safety and Health Training.



(Cover artwork courtesy of Eric Guerrero)

“It was a very helpful meeting,” said Chip Hughes, director WETP. “NIEHS was lauded for filling a critical niche in preparing potential responders. Numerous suggestions for adding to the draft content and developing pre-event training opportunities were voiced by meeting participants. A revised draft of the training tool will be shared with meeting participants and then web posted for use by the broader disaster preparedness community.”

Participants from the NIEHS WETP awardee community included the Western Regional Universities Consortium, Center for Construction Research and Training, International Union of Operating Engineers, Laborers-AGC (Associated General Contractors of America) Education and Training Fund, Midwest Consortium, Hazardous Material Training and Research Institute, Inc., International Chemical Workers Union and OAI, Inc. Other important groups such the East Bay Municipal Utility District, California Department of Public Health, California Division of Environmental and Occupational Disease Control and California Seismic Safety Commission also provided excellent comments and suggestions for changes to the training tool.

WETP has previously developed similar training tools in response to hurricanes, wildfires, radiological dispersion devices (dirty bombs), avian flu and floods.

Under the National Response Framework, the NIEHS Worker Education and Training Program may be activated to provide safety and health training and technical assistance to disaster responders. To date, WETP has been activated under the National Response Framework twice: following Hurricanes Katrina and Rita and during the California wildfires in 2007. The NIEHS WETP also has a long history of involvement in disaster response activities, including the Oklahoma City bombing, the World Trade Center attacks and the anthrax attacks, among others.

The Western Region Universities Consortium, based at the UCLA Labor Occupational Safety and Health Program, includes Arizona State University, University of California at Berkeley Labor Occupational Health Program, University of California Davis Extension and University of Washington/Northwest Center for Occupational Health and Safety.

Contacts: Ted Outwater at outwater@niehs.nih.gov
Jim Remington at remingonj@niehs.nih.gov

Extramural Papers of the Month

By Jerry Phelps

Discovery of a Shape-Shifting Protein Could Lead to Anti-Bacterial Agent

A small molecule that locks the shape of the enzyme porphobilinogen synthase (PBGS) into an inactive form could one day form the basis of a new species-specific antibiotic, according to NIEHS-supported researchers. Their work may offer insight into ways of combating multidrug resistance.

PBGS is crucial for energy metabolism in nearly all organisms. To be activated, it must have two subunits added to the six-subunit molecule, or hexamer configuration, which makes up its basic form. The research team discovered a small molecule, Morphlock-1, which binds to the inactive form of the enzyme and locks the enzyme in a hexamer shape, thus preventing the rearrangement of the molecule and the addition of the two additional subunits required for activation.

While this study utilized a form of the enzyme found in peas, the researchers believe that this principle could apply to bacterial versions of the enzyme as well. Current research is aimed at fine tuning the structure of Morphlock-1 so that it blocks only the bacterial version of the enzyme and not other cells.

The researchers said they hope to develop a suite of drugs that will stabilize the PBGS hexamer in order to prevent bacteria from developing complete resistance to a cocktail of such compounds.

Citation: Lawrence SH, Ramirez UD, Tang L, Fazliyez F, Kundrat L, Markham GD, Jaffe EK. 2008. Shape shifting leads to small-molecule allosteric drug discovery. *Chem Biol* 15(6):586-596.

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Maternal Smoking and Receptor Gene Variant Combine to Increase Risk for Childhood Asthma

Exposure to *in utero* maternal smoking and childhood second-hand smoke are associated with wheezing, a common symptom of asthma, according to a new study from NIEHS-funded investigators at the University of Southern California. However, children who were homozygous for a single nucleotide polymorphism in the beta2-adrenergic receptor and who were exposed to maternal smoking *in utero* were three times more likely to develop asthma symptoms compared to unexposed children without the altered gene. Similar effects were evident for exposure to second-hand smoke during childhood.

Additionally, as the number of smokers increased in the home, the risk for symptoms increased for children with the gene polymorphism. The researchers examined two cohorts of children recruited in 1993 and 1996 and found similar results. The 3,128 non-Hispanic and Hispanic white children were participants in the Children's Health Study.

These results suggest that because of the high prevalence of asthma in children, intervention strategies are critically needed to reduce smoke exposures to children in general and especially those who are genetically susceptible to the adverse effects of exposure to second-hand smoke.

Citation: Wang C, Salam MT, Islam T, Wenten M, Gauderman WJ, Gilliland FD. 2008. Effects of *in utero* and childhood tobacco smoke exposure and beta2-adrenergic receptor genotype on childhood asthma and wheezing. *Pediatrics* 122(1):e107-114.

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Single Nucleotide Polymorphism is Associated with Neuroblastoma

Using a genome-wide association study, NIEHS-funded researchers identified an association between neuroblastoma and three common single-nucleotide polymorphisms. Homozygosity for the most significantly associated polymorphism increased the risk of neuroblastoma two-fold.

Neuroblastoma is the most common cancer in infancy, with about half of neuroblastoma cases occurring in children younger than two years old. It is a neuroendocrine cancer arising from any neural crest element of the sympathetic nervous system. Solid tumors, which take the form of a lump or mass, commonly begin in one of the adrenal glands, though they can also develop in nerve tissues in the neck, chest, abdomen or pelvis.

A genome-wide association study is an examination of genetic variation across the human genome, designed to identify genetic associations with observable traits, such as blood pressure or weight, or why some people get a disease or condition.

Additional results from the study show that children who were homozygous for the three identified polymorphisms were more likely to have metastatic disease and disease relapse. The polymorphisms could be used to identify children at risk for neuroblastoma or those who are likely to have a poor prognosis and therefore may need more aggressive treatment.

Citation: Maris JM, Mosse YP, Bradfield JP, Hou C, Monni S, Scott RH, Asgharzadeh S, Attiyeh EF, Diskin SJ, Laudenslager M, Winter C, Cole KA, Glessner JT, Kim C, Frackelton EC, Casalunovo T, Eckert AW, Capasso M, Rappaport EF, McConville C, London WB, Seeger RC, Rahman N, Devoto M, Grant SF, Li H, Hakonarson H. 2008. Chromosome 6p22 locus associated with clinically aggressive neuroblastoma. *N Engl J Med* 358(24):2585-2593.

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Epigenetic Markers Change Over a Lifetime

New findings about the epigenetic markers on an individual's DNA may explain why some people become more susceptible to disease as they age and why individual disease risk is similar within families. NIEHS-funded researchers found that certain DNA methylation patterns or epigenetic markers change during a person's lifetime and the amount of change is similar among related people.

The research team analyzed DNA methylation in more than 200 individuals from two cohorts of subjects. Samples of DNA, taken 11 years apart, were analyzed from an Icelandic population. One third of them had significant changes in their DNA methylation; some higher, some lower. This change over time represents a proof-of-principle that an individual's epigenetics does change with age. A Salt Lake City cohort was made up of two and three generation families whose DNA was sampled 16 years apart. The results showed that DNA methylation changes tended to be similar among family members.

The authors concluded that “the implications of these results are potentially profound for population-based studies of human disease.” The epigenetic changes seen over time might directly influence the onset or progression of disease and might also reflect age-related or environmental exposures.

Citation: Bjornsson HT, Sigurdsson MI, Fallin MD, Irizarry RA, Aspelund T, Cui H, Yu W, Rongione MA, Ekström TJ, Harris TB, Launer LJ, Eiriksdottir G, Leppert MF, Sapienza C, Gudnason V, Feinberg AP. 2008. Intra-individual change over time in DNA methylation with familial clustering. *JAMA* 299(24):2877-2883.

(Jerry Phelps is a program analyst in the Program Analysis Branch of 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

The Binding of Cell-Surface Nucleolin and P-selectin Promotes Metastasis

NIEHS scientists determined that the cell-surface form of nucleolin binds P-selectin — a vascular adhesion molecule — to the surface of Colo-320 human colon carcinoma cells; this binding leads to the activation of signal transduction pathways that promote tumor cell metastasis. Generally, the protein nucleolin exists inside the cell and shuttles between the nucleus and the cytoplasm, but the cell-surface form of nucleolin acts as a P-selectin receptor molecule. This work sheds light on how cancer cells establish new colonies at distant sites in the body.

The team used affinity chromatography, mass spectrometry, immunoblots and RNAi knockdown to identify cell-surface nucleolin as a P-selectin receptor on Colo-320 cells. The data indicated P-selectin binding to the cell initiated the phosphoinositide-3 kinase and p38 mitogen-activated protein kinase signaling pathways, which in turn activated the transmembrane glycoprotein $\alpha 5\beta 1$ integrin. These actions resulted in the increase of cell attachment and cell spreading on fibronectin substrates.

The finding that cell-surface nucleolin is a P-selectin receptor is a novel discovery and provides a potential target for therapeutics that inhibit the progress of metastatic disease.

Citation: Reyes-Reyes EM, Akiyama SK. 2008. Cell-surface nucleolin is a signal transducing P-selectin binding protein for human colon carcinoma cells. *Exp Cells Res* 314(11-12):2212-2223.

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NOS and Nitroglycerin-mediated Vasodilation

Nitroglycerin helps patients with angina and a past history of heart attacks by relaxing the smooth muscles around blood vessels, allowing more blood to reach cardiac muscles, but the exact mechanism involved in nitric oxide synthase (NOS) activation was unknown. Researchers at NIEHS and the University of Sao Paulo School of Medicine have found evidence that nitroglycerin triggered constitutive NOS activation using cell cultures, isolated vessels and whole animals. The work may offer insight into the molecular mechanisms involved in nitrate resistance.

The team's studies indicated that endothelial NOS was phosphorylated at Ser1177 on the endothelial isoform and Ser852 on the neuronal isoform in the aortae of mice and rats treated with nitroglycerin, which confirmed that isoforms of NOS were involved in vasorelaxation. Aortic ring studies determined that high doses of nitroglycerin (300 nm) produced vasodilation that was independent of the endothelium and could not be annulled by NOS inhibitors. At higher doses nitroglycerin is known to be bioactivated to nitric oxide.

Citation: [Bonini MG](#), [Stadler K](#), [Silva Sde O](#), [Corbett J](#), [Dore M](#), [Petranka J](#), [Fernandes DC](#), [Tanaka LY](#), [Duma D](#), [Laurindo FR](#), [Mason RP](#). 2008. Constitutive nitric oxide synthase activation is a significant route for nitroglycerin-mediated vasodilation. *Proc Natl Acad Sci USA* 105(25):8569-8574.

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The Involvement of the MEK-MSK1 Pathway in the Immune Response

According to NIEHS scientists, farnesol, an isoprenoid alcohol used as a flavoring ingredient, induces the expression of several inflammatory genes in human lung adenocarcinoma H460 cells including IL-6, CXCL3, IL-1 α and COX-2. The response was dependent on the NF- κ B pathway and involved the MEK1/2-ERK1/2-MSK1-dependent phosphorylation of p65/RelA (Ser276).

The researchers utilized microarray analysis, western blots, siRNA knockdowns and electrophoretic mobility shift assay (EMSA). One of the findings of the studies demonstrated that the farnesol treatment reduced the level of I κ B α protein and overexpression of several immune response and inflammatory genes. The results also suggest that activation of the NF- κ B pathway by farnesol is part of a pro-cell survival response.

Citation: [Joo JH](#), [Jetten AM](#). 2008. NF-kappaB-dependent transcriptional activation in lung carcinoma cells by farnesol involves p65/RelA(Ser276) phosphorylation via the MEK-MSK1 signaling pathway. *J Biol Chem* 283(24):16391-16399.

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Low Doses of UVA Promote Tumor Growth in Human Keratinocytes

Extended exposure to the sun has long been associated with human skin cancer, but researchers at NIEHS have found that low, nonlethal doses of UVA (315–400nm) — a wavelength of light that makes up 95% of the UV irradiation in natural sunlight — induces dose-dependent cell cycle progression in human HaCaT keratinocytes. The study, performed by NIEHS scientists, provided evidence that even low amounts of UVA could promote skin cancer and that the mechanism involved disintegrin and metalloprotease/epidermal growth factor receptor (EGFR)/AKT/Cyclin D1 pathways.

The research team, who used siRNA knockdowns, western blotting and confocal microscopy, determined that AKT activation was mediated by the EGFR pathway following UVA exposure. In addition, knockdown of cyclin D1 reduced the G1-S transition triggered by UVA exposure, which indicated cyclin D1's role in the process. The study also discovered that the metalloprotease ADAM proteins were also involved in cell cycle progression because the use of a metalloprotease inhibitor prevented cell cycle progression after UVA exposure.

The authors acknowledged that other signaling pathways may be involved in UVA-induced cell proliferation, but concluded that the ADAM/EGFR/AKT pathway was required. The work may further the development of safe and effective chemopreventative and therapeutic strategies for skin cancer.

Citation: [He YY](#), [Council SE](#), [Feng L](#), [Chignell CF](#). 2008. UVA-induced cell cycle progression is mediated by a disintegrin and metalloprotease/epidermal growth factor receptor/AKT/Cyclin D1 pathways in keratinocytes. *Cancer Res* 68(10):3752-3758.

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Inside the Institute

NIEHS Takes on the Triangle Triathlon in Style

By Shannon Baker

“I’m retired,” stated trainer and NIEHS scientist Matthew McElwee after finishing the grueling Triangle Triathlon 2008 July 13 at Lake Crabtree. McElwee is a predoctoral fellow in the NIEHS [Comparative Genomics Group](#). He, along with three of his lab mates, Staff Scientist Elena Braithwaite, Ph.D., Predoctoral Fellow Brooke Tvermoes, and Research Assistant Daniel Snyder, took on the challenge of competing in the event, a USA-sanctioned race featuring a 750-meter swim, 15-mile bike ride and 5K run.

The event began at 7:30 a.m. with 738 eager participants. By the end of the fray, the NIEHS team had ample reason to be proud of their performance — and McElwee could certainly justify resting on his laurels in well-deserved retirement from competitive racing.

Training for the group began months prior to the event when McElwee designed a rigorous workout regimen for his teammates with exercises tailored to help them prepare for the day’s event. McElwee and Tvermoes are no strangers to triathlon competitions. Both have participated in local triathlon and Ironman competitions. This year the veterans were joined by newcomers Braithwaite and Snyder.

July’s record breaking heat didn’t stop the NIEHS team from breaking records. “The heat wasn’t bad, probably because we were so busy,” Braithwaite explained afterwards. Tvermoes came in 4th place in the Overall Women category with a time of 1:11:38. The Novice category celebrates achievement for first time competitors, and Braithwaite came in an enviable 6th place in the division for women. Snyder broke into the Novice category for men, placing 5th.

Several lab members and NIEHS employees came out to cheer on their fellow co-workers and friends. “I think this experience was so fun because we did this as a team and that makes all the difference,” Braithwaite remarked. Recalling the ups and downs of the day, McElwee noted that there had been a bike accident between two riders that left one unconscious. The 2008 race proved to be an especially competitive one for the Triangle Triathlon.

After the race was over, Tvermoes hosted a barbeque in celebration of the day’s achievements. When asked if they would ever do another triathlon together, they said in unison, “We are planning one for September.” McElwee added, “Maybe I’m really more semi-retired.”

(Shannon Baker is a rising senior at Peace College in Raleigh who spent a three-week internship in the NIEHS Office of Communication and Public Liaison. She is currently working part time in the NIEHS Office of the Director.)



The team members, from left to right, Braithwaite, Tvermoes and McElwee, were interviewed in their lab office two weeks before the competition. At that point, Braithwaite was still apprehensive, little knowing how well she would do in the triathlon. Snyder, not shown, was unable to participate in the interview. (Photo courtesy of Steve McCaw)

Veteran Researcher Colin Chignell Dies Unexpectedly

By Eddy Ball

NIEHS chemist Colin Chignell, Ph.D., died unexpectedly July 16 at age 70 in a drowning accident near North Myrtle Beach, S.C. while on a family vacation. An NIH employee for 42 years, Chignell was a principal investigator in the Photosensitization Reactions Group in the NIEHS Laboratory of Pharmacology at the time of his death.

After receiving his Ph.D. in medicinal chemistry from the University of London in 1962, Chignell came to NIH as a visiting fellow. He served as one of the first National Institute of General Medical Sciences research associates in Pharmacology and Toxicology, a position he held from 1962 to 1965. Afterwards, he was a research pharmacologist in the Molecular Pharmacology Section, Pulmonary Branch, of the National Heart, Lung and Blood Institute prior to joining NIEHS in 1977.

Chignell published more than 220 peer-reviewed articles in leading biomedical journals, as well as more than 30 book chapters and reviews. Among his many honors, he was awarded the John J. Abel prize by the American Society for Pharmacology and Experimental Therapeutics (ASPET). He was recently named an associate editor of the *Journal of Photochemistry and Photobiology*.

Chignell was respected and well liked among his colleagues at NIEHS for his transformative research and collegial manner. In a tribute following his death, his long-time friend, colleague and supervisor at NIEHS, John Pritchard, Ph.D., praised Chignell for his work “at the forefront of a revolution in pharmacology that sought to understand the molecular basis of pharmacological activity.” Pritchard, who is chief of the Laboratory of Pharmacology, also lauded Chignell’s insights into photosensitization and free radical biology, as well as a managerial style Pritchard described as “always nurturing and supportive.”

Trainees in his lab deeply appreciated Chignell’s mastery of his field and the quality of his mentoring and advising. Chignell also had devoted colleagues in the academic community who returned year after year to work with him as research associates in the Summers of Discovery program — and felt that their experiences in his lab significantly impacted the quality of their teaching.

NIEHS Acting Director Sam Wilson, M.D., described the impact of Chignell’s contributions to the Institute’s mission. “Throughout his long and productive career, Colin was committed to the pursuit of scientific excellence, and he was an important part of the extraordinary research team here at NIEHS,” Wilson said. “He will be missed by his many friends throughout the scientific community.”

Many of Chignell’s colleagues joined his family and friends at a funeral service held July 23 in Cary, N.C. Chignell is survived by his wife, Anke, two children and two grandchildren.



Principal Investigator Colin Chignell
(Photo courtesy of Steve McCaw)

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