National Institute of Environmental Health Sciences

Environmental Factor

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April 2014

NIEHS Spotlight

SOT 2014 — packed with good science, energy, and enthusiasm

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Workshop advances arsenic research and prevention

NIEHS hosted a meeting March 3-4 that gave scientists across a range of disciplines a venue for laying the foundation for the next generation of arsenic research.

A visit from the Dalai Lama — not an ordinary science talk Video

The Dalai Lama visited NIH March 7 to discuss the role of science in human flourishing as part of the J. Edward Rall Cultural Lecture.

Spirit Lecture features UNC Chancellor Carol Folt Video

NIEHS welcomed University of North Carolina at Chapel Hill Chancellor Carol Folt, Ph.D., March 20 to present the 2014 Spirit Lecture in Rodbell Auditorium.

NIH celebrates equity, diversity, and inclusion

NIH officially launched the new Office of Equity, Diversity, and Inclusion with a full schedule of activities March 24-27 that included a special flash mentoring session at NIEHS.

Science Notebook

Distinguished lecture highlights RNA discoveries

Melissa Moore, Ph.D., sheds new light on how RNA is transported at the cellular level and diseases that can result when the process goes awry.

Cholesterol gene may be responsible for increased inflammation

In the first paper to result from the Environmental Polymorphisms Registry, NIEHS researchers find the APOE4 gene contributes to inflammation risk.

Prevalence of allergies the same, regardless of where you live

In largest, most comprehensive U.S. study to date, NIEHS scientists find allergy prevalence is consistent, except in children under 6.

Obesity primes the colon for cancer

NIEHS scientists, studying a gene thought to be protective of colon cancer, discovered that obesity, not diet, causes changes in the colon that may lead to colorectal cancer.

Solving a mystery Video

In a March 5 seminar at NIEHS, Richard Peterson, Ph.D., presented pioneering work that implicated dioxin in pesticides in the mysterious disappearance of fish in Lake Ontario.

NIEHS Spotlight

Roundtable explores benefits and challenges of data sharing

The Institute of Medicine hosted a roundtable March 19 to explored the benefits and challenges of sharing of environmental health sciences data.

Seminar explores communication of uncertainty and risk

For insight into how to better express its conclusions on potential health concerns, NTP turned to two experts in psychology during a March 12 seminar at NIEHS.

Scientists inaugurate inflammation faculty

The faculty will enhance cross-cutting research on environmentally associated inflammation, involved in some increasingly prevalent diseases.

Regional symposium addresses reproductive biology

Regional researchers and trainees connected at the March 8 annual symposium of the Triangle Consortium for Reproductive Biology.

Trainees shine at reproductive biology symposium

Research and training at NIEHS received recognition at a symposium March 8, with two NIEHS trainees winning top awards for their presentations.

UNC Superfund scientists study effects of Dan River coal ash spill Video

Damian Shea, Ph.D. and colleagues are collecting and analyzing samples from the Dan River to determine the potential for human exposure.

Science Notebook

New study links BPA and prostate cancer in humans

Researchers funded in part by NIEHS report higher urinary concentrations of BPA in men with prostate cancer than in men without the disease, and that low-dose BPA may contribute to disease progression.

Symposium explores cognitive effects of neurotoxic exposures during development

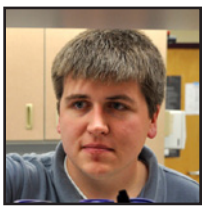
The Duke University Integrated Toxicology and Environmental Health Program held its spring symposium March 7 on the Duke campus in Durham, N.C.

Lecture highlights flame retardants

In a March 19 lecture, Heather Stapleton, Ph.D. presented studies of human exposure to flame-retardants and potential endocrine-disrupting effects.

Silicone wristbands facilitate exposome study

NIEHS-funded Superfund researchers at Oregon State University, led by Kim Anderson, Ph.D., have developed a simple wristband and extraction method that can test exposure to 1,200 chemicals.



Osteoporosis drug may treat breast and liver cancers

NIEHS-funded researchers determine that raloxifene binds with the aryl hydrocarbon receptor, killing cancer cells that do not have receptors for estrogen.

NIEHS Spotlight

Building global partnerships to improve research communication

In March, NIEHS Global Environmental Health program coordinator Banalata (Bono) Sen, PhD., led a seminar in India as part of the Institute's commitment to international collaborations.

Collaboration, focus, and innovation keys to replacing animal use

NTP's Warren Casey, Ph.D., keynotes a conference on effective alternatives to use of animals in toxicology research, presented by the N.J. Association for Biomedical Research.

Duke and UNC SRP scientists connect with journalists

The NIEHS-funded Duke and UNC Superfund Research Program Research Translation Cores co-hosted a workshop March 5-6, focused on communicating science to the media.

NTP holds flash mentoring session for trainees

NTP caught a flash wave that's been sweeping NIH recently, with a mentoring and poster session for trainees March 20 in Rodbell Auditorium.

Inside the Institute

NIEHS to upgrade exterior lighting to LED

The Institute is replacing lights on its roadways with LED lights, saving on both energy and cost.

Science Notebook

Community resilience and disaster response in the U.S. Gulf Coast

Along the Gulf Coast, NIEHS-funded researchers study the factors that contribute to community resiliency after disasters and the best ways to build resilience.

Webinar advances review of TCE

NTP hosted a webinar March 17 to obtain scientific input to exposure assessment issues and public input on protocol for its review of TCE.

NIEHS scientists contribute to advance in urinary bladder cancer research

Dmitri Gordenin, Ph.D., and colleagues reported in Nature their analysis of molecular alterations in urothelial bladder carcinomas, identifying potential therapeutic targets.

Jetten explores the role of Glis proteins in development and disease

Anton Jetten, Ph.D., discussed findings related to Glis proteins and their role in diseases such as diabetes and kidney disease in a March 4 talk at NCSU.

This month in EHP

The April issue of Environmental Health Perspectives highlights concerns with lead in decorative paints, and impacts of the Navajo Nation owning coal mines on its land.

Calendar of Upcoming Events

- **April 3**, NIH webcast, 10:00 a.m. – noon — National Native American Heritage 2014 Speaker Series, featuring presentations by Dawn Satterfield, R.N., Ph.D., CDC, and Lawrence Agodoa, M.D., NIDDK
- **April 3 (offsite event)**, in room C113 at the U.S. Environmental Protection Agency (EPA) in Research Triangle Park, N.C,., 10:00-11:30 a.m. — NIEHS/EPA seminar on "Exposure Science in the 21st Century: A Vision, a Strategy, and New Directions in 2014," by Paul Lioy, Ph.D.
- **April 3**, in Rodbell Auditorium, 3:00 – 4:00 p.m. — Karen Wetterhahn Memorial Award Seminar Series, featuring a presentation by Nicki Baker, Ph.D., on "Polychlorinated Biphenyl Ligands of the Aryl Hydrocarbon Receptor Promote Diabetes"
- **April 9**, webinar, 1:00 – 2:30 p.m. — EPA/NIEHS Children's Centers 2014 Webinar Series, Registration
- **April 14**, in Rodbell Auditorium, 11:00 – noon — Hans L. Falk Lecture, " The Evolutionary History of Steroid Hormone Receptors: Ancient Insights Into Endocrine Disruption," by Joseph Thornton, Ph.D.
- **April 15**, webinar, 1:00 – 2:00 p.m. — Superfund Research Program Trainee Webinar Series, featuring Minghui Gui of the University of Kentucky, and Fabian Grimm of the University of Iowa, Registration
- **April 16-18**, in Rodbell Auditorium, 8:00 a.m. – 5:00 p.m. — NTP Board of Scientific Counselors meeting
- **April 25 (offsite event)**, at the EPA conference center, 7:45 a.m. – 4:45 p.m. — 17th Annual NIEHS Biomedical Career Symposium, Registration
- **April 28-29**, in Rodbell Auditorium, 8:00 a.m. – 5:00 p.m. — Outstanding New Environmental Scientist awardees conference
- **April 30**, webinar, 1:00 – 2:00 p.m. — Superfund Research Program Trainee Webinar Series, featuring Jing Sun of Columbia University, and Peter Wagner of Harvard University, Registration
- **May 1**, in Rodbell Auditorium, 8:00 a.m. – 5:00 p.m. — NIEHS Genomics Day
- View More Events: NIEHS Public Calendar

Extramural Research

Extramural papers of the month

- Preterm birth might increase risk for type 2 diabetes
- DDT metabolite linked to higher Alzheimer's risk
- Phthalate exposure trends from 2001 to 2010
- Grasp protein aids protective function of p53 in skin

Intramural Research

Intramural papers of the month

- Allergy prevalence the same in U.S., no matter where you live
- DNA polymerase mu has a novel mechanism for binding DNA
- MBD3 studies suggest NuRD complex regulates chromatin structure
- MicroRNA expression levels differ in breast cancer patients

NIEHS Spotlight

SOT 2014 — packed with good science, energy, and enthusiasm

By Robin Mackar

When the 53rd annual meeting of the Society of Toxicology (SOT) in Phoenix concluded March 27, there was a consensus among the NIEHS and NTP delegation that it fulfilled its mission of showcasing cutting-edge science and providing opportunities for people to network and form new collaborations.

Birnbaum, right, and Lehman-McKeeman at the official signing of the MOU between NIEHS and SOT. (Photo courtesy of Robin Mackar)

Memorandum of understanding signed

Among the more formal collaborative events at this year's conference was the signing of a memorandum of understanding (MOU) between SOT and NIEHS, at a preconvention ceremony Sunday afternoon, March 23. The signing set forth a framework for an alliance between NIEHS and SOT, to foster a shared dedication to provide global leadership toward creating a safer and healthier world, by increasing the impact of the science of toxicology.

"We've always had a very good working relationship with SOT, but this memorandum will provide us with even more opportunities to collaborate, as we both work to identify, characterize, and prevent diseases associated with the environment," said NIEHS and NTP Director Linda Birnbaum, Ph.D., as she signed the document with SOT president Lois Lehman-McKeeman, Ph.D.

Annette Kirshner, Ph.D., right, of DERT, played a lead role in setting up the successful NIEHS resource funding room. Above, she is shown at the NIEHS exhibit helping Michael Aschner, Ph.D., a grantee from Albert Einstein College of Medicine of Yeshiva University. (Photo courtesy of Robin Mackar)

Enthusiasm for science

The sunny, warm weather at the meeting might be one factor that contributed to the enthusiasm for the meeting, but another was the presence of many talented high school, undergraduate, graduate, and postdoctoral students who were at many of the sessions asking forward-thinking questions.

The students were engaged during an undergraduate program offered Sunday, as Birnbaum talked about her own winding career path.

They were also very vocal at the Monday afternoon featured session, "A Conversation with the Director of NIEHS," chaired by Norbert Kaminski, Ph.D., of Michigan State University.

The format of the session was conversational and welcoming. With Birnbaum and Kaminski seated on stage, and about 200 people in attendance, there were no slides, creating an environment that encouraged audience participation.

A few questions from Kaminski about the NIEHS budget and strategic plan kicked off the conversation, which was soon followed by questions from the audience. Queries ranged from predictive toxicity efforts, arsenic, and droughts, to peer review of grants and the new collaboration between NIEHS and the World Health Organization. Birnbaum thoughtfully addressed each question.

"I'm thrilled to see so many undergraduates here," Birnbaum said, as many made their way to the podium. One asked about some of the challenges Birnbaum faced as she developed her own career path and what advice she would offer to students.

"Always be willing to try something new," she said. "Try working with a new collaborator, try out your crazy ideas, and don't be afraid to fail. Failure can teach us valuable lessons."

Birnbaum ended the informal session by announcing that NIEHS is searching for a new editor-in-chief for the journal Environmental Health Perspectives. Hugh Tilson, Ph.D., who has held the position since 2007, recently announced his retirement.

Funding room and exhibitor hosted sessions

In addition to the numerous posters and talks by NIEHS and NTP scientists, the NIEHS resource funding room proved very popular. Division of Extramural Research and Training (DERT) program representatives staffed the room for two days, providing one-on-one-consultation for individuals interested in grants and training.

The two Institute exhibitor-hosted sessions were also a success. Mark Cesta, D.V.M., Ph.D., showcased the Nonneoplastic Lesion Atlas, the newest resource from

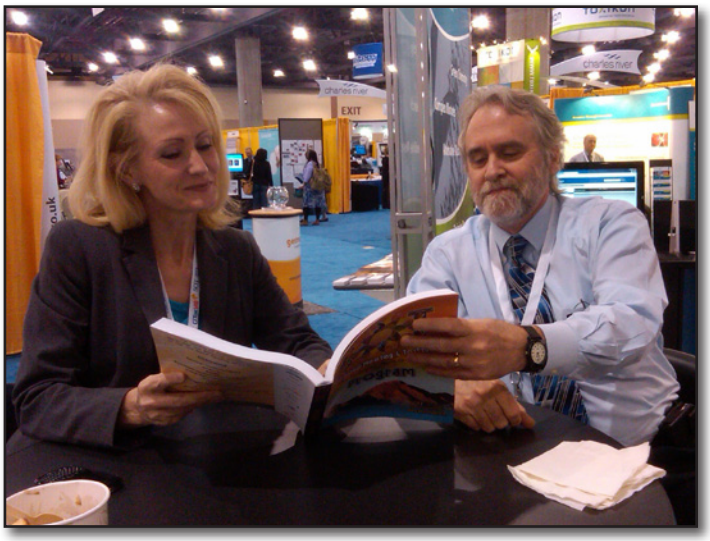
At the yearly SOT meeting, toxicologists get to make new acquaintances and meet up with colleagues from the past. Birnbaum, right, is shown sharing information and smiles with Michael Gallo, Ph.D., of Robert Wood Johnson Medical School at the University of Medicine and Dentistry of New Jersey. (Photo courtesy of Robin Mackar)

At the MOU signing ceremony, Nigel Walker, Ph.D., of NTP, center, joined with Birnbaum, left, and Dori Germolec, Ph.D., who is an SOT Counselor. (Photo courtesy of Robin Mackar)

Walker had fun catching up with some former NTP colleagues, Angelique Braen, Ph.D., left, of Ikaria Inc., and Ed Garner, Ph.D., right, of Oso Corredor Scientific Consulting. (Photo courtesy of Robin Mackar)

NTP, and Allen Dearry, Ph.D., NIEHS Office of Scientific Information Management director, led a session on "Advancing Environmental Health Data Sharing and Analysis."

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



Christine Flowers, left, NIEHS communications director, and Pat Mastin, Ph.D., of DERT, look over the SOT program, to decide what to attend next. Flowers oversaw the design of the popular NIEHS exhibit. (Photo courtesy of Robin Mackar)

Becky Boyles, Ph.D., left, of the NIEHS Office of Scientific Information Management, talked to researchers about data sharing activities. (Photo courtesy of Robin Mackar)

Tilson talked to many people at SOT about the editor-in-chief role he is about to leave. He announced his retirement in March after 40 years of federal service. Efforts are underway to fill this important position. (Photo courtesy of Robin Mackar)

Tammy Collins, Ph.D., left, who leads the NIEHS Office of Fellows' Career Development, was very busy during the conference, talking to many postdocs about positions at NIEHS and NTP. (Photo courtesy of Robin Mackar)

Although the meeting was packed with science talks, some found time to explore the beauty of Phoenix. This hummingbird was having breakfast at the botanical gardens. (Photo courtesy of Nigel Walker)

Toxicology Liaison Chris Weis, Ph.D., left, and Congressional Affairs Liaison Mary Gant, from the NIEHS Bethesda, Md., office, conducted and attended a few of the sessions at SOT. (Photo courtesy of Nigel Walker)

Michael DeVito, Ph.D., left, of NTP, took time to talk to some of the enthusiastic students eager to hear about NTP work currently underway and get advice on choosing a career path. (Photo courtesy of Robin Mackar)

Cesta, left, showed many people, including fellow NTP toxicologist Scott Auerbach, Ph.D, the capabilities of the new NTP Nonneoplastic Lesion Atlas. Auerbach was sought out by many to talk about predictive toxicology efforts at NTP. (Photo courtesy of Robin Mackar)

Jonathan Hollander, Ph.D., left, and Mike Humble, Ph.D., right, of DERT, talked about funding opportunities with Wade Powell, Ph.D., of Kenyon College, in the NIEHS funding resource room. (Photo courtesy of Robin Mackar)

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Workshop advances arsenic research and prevention

By Eddy Ball

The NIEHS Superfund Research Program (SRP) hosted a meeting March 3-4 that gave scientists across a range of disciplines a venue for laying the foundation for the next generation of arsenic research.

The "Health Effects and Mitigation of Arsenic: Current Research Efforts and Future Directions" workshop attracted nearly 150 leading experts from universities and other organizations throughout the world, as well as scientists from NIEHS, NTP, and the U.S. Environmental Protection Agency (EPA). The participants worked toward a common goal — to better understand how low levels of arsenic impact human health, and how to best prevent exposure to arsenic, whether it occurs naturally or as a consequence of human activity.

Carlin managed to give all scheduled speakers an opportunity to present their research findings. Her quick thinking and engaging sense of humor helped ensure that the meeting ran smoothly, in spite of cancellations due to the inclement weather. (Photo courtesy of Steve McCaw)

Speakers reported findings from their work in labs, through cohort studies of mothers and children, and with prevention and remediation efforts on the ground, from abandoned mines in the southwestern U.S. to arsenic hotspots in Asia, Mexico, and South America.

NIEHS Health Scientist Administrator Danielle Carlin, Ph.D., led the careful planning behind the workshop and responded quickly to an unexpected snowstorm, which forced cancellation of the panel discussions and squeezed two full days of work into two five-hour sessions.

Despite the many other demands on her time, Birnbaum was on hand for the entire program. "This was a great workshop," she said afterwards. (Photo courtesy of Steve McCaw)

Charting a course for arsenic work to come

In her opening comments, NIEHS and NTP Director Linda Birnbaum, Ph.D., set the tone for the presentations and panel discussions planned for the two-day meeting. She underscored the global extent of the problem; described the importance of a transdisciplinary approach for SRP projects, in both work underway and planned for the future; and shared new insights into the health threats posed by exposure to arsenic.

"Pretty much every system [of the body] is involved," she said, adding that the fundamental question of dose has yet to be answered satisfactorily. "How much is too much?" she asked, referring to the dramatic reassessment of U.S. regulatory standards in 2006, lowering the so-called safe level in water from 50 to 10 micrograms per liter — a standard most of her listeners still consider much too lenient.

Birnbaum concluded by issuing the workshop a challenge — to determine the current state of the science in arsenic research and identify the knowledge gaps that will inform future arsenic research programs.

Among the giants in arsenic research and prevention

The workshop's keynote speaker, University of North Carolina at Chapel Hill (UNC) Chancellor Carol Folt, Ph.D., kicked off 22 presentations by scientists from the world's leading research organizations. Folt's colleagues at Dartmouth College joined their counterparts from the University of Arizona (UA), Columbia University, and several other biomedical research centers, to update others on their accomplishments, challenges, and ongoing struggles, especially in the area of compliance with remediation programs.

Topics ranged from engineering innovations to reduce deposits of arsenic from irrigation in rice fields, mode of action, and speciation, to longitudinal studies of the association of early exposures with diseases developing late in life, due to epigenetic modifications of gene expression. Presentations also addressed multiple sources of exposure, remediation strategies, and stabilization of abandoned mining sites with vegetative cover.

In the meeting's final presentation, Columbia University geochemist Alexander van Geen, Ph.D., described some of the frustration his team has experienced with compliance in their work in Asia, helping residents find and use arsenic-free sources of water by translating research into prevention.

"It's a cycle of excitement and disappointment," he said. "We've been there more than a decade and the problem hasn't gone away."

Moving forward

NIEHS SRP Director Bill Suk, Ph.D., concluded the meeting with final thoughts. "This [widespread exposure to arsenic] is a significant global health problem that can only be effectively addressed by approaches that are cross-disciplinary, multidisciplinary, and transdisciplinary," he said.

Suk pointed to questions that still need to be answered in terms of launching more effective strategies for prevention, explicating major exposure routes, raising community awareness, and addressing the role of government, business, and industries in preventable exposures to arsenic.

Superfund — shaping scientific research and scientific careers

In her keynote address, Folt wove her vision for the future of arsenic work into her personal history, with a presentation on "Arsenic and Children's Health: A Multidisciplinary Approach From Superfund to Children's Centers." She was the first of many speakers who praised the NIEHS SRP for its pioneering support of interdisciplinary arsenic research.

Folt also credited SRP with helping shape her career as a woman scientist and leader in a field long dominated by men. By mandating a broad approach to complex problems, and by emphasizing translation and problem solving, she said, SRP promoted diversity and teamwork, challenged academic hierarchy, and required scientists to communicate their research to people affected by environmental exposures.

SRP continues to be a driving force behind big science, Folt said. As a result, she added, "We [now] have to talk about convergent science."

As van Geen noted in his presentation on reducing arsenic exposure from drinking well water in South and Southeast Asia, SRP also remains the primary funder of this kind of research, despite growing support from other organizations.

"The level of support by SRP has not been matched by any of the others," he told the audience, as he acknowledged some recent support from the National Science Foundation, U.S. Agency for International Development, and the U.K. Department for International Development.

As the meeting came to a close, attendees looked forward to new collaborations and workshop products, including a published commentary and an upcoming series of webinars.

On her way to the podium, Folt embraced Birnbaum, who had donned a UNC Carolina-blue cap to introduce the keynote speaker. Folt retuned to NIEHS Mar. 20 to present the 13th annual Spirit Lecture. (Photo courtesy of Steve McCaw)

Each of the workshop's four sessions was moderated by an EPA scientist. Following his talk in the global environmental cycling and bioavailability session, North Carolina State University soil scientist Matt Polizzotto, Ph.D., left, joined moderator Karen Bradham, Ph.D., for questions. (Photo courtesy of Steve McCaw)

Among NTP and NIEHS scientists at the meeting was biologist Erik Tokar, Ph.D., who is part of the NTP Laboratories Inorganic Toxicology Group, headed by Mike Waalkes, Ph.D. Waalkes' group has produced several of the seminal studies on arsenic that were referenced by presenters. (Photo courtesy of Steve McCaw)

Among the leading figures in arsenic research and remediation at the workshop were, from left, UA emeritus professor of molecular and cell biology Vasken Aposhian, Ph.D.; pharmacologist Joseph Graziano, Ph.D., of Columbia University; UA environmental microbiologist and SRP Director Raina Maier, PhD.; and nutritional biochemist Mary Gamble, Ph.D., of Columbia University. (Photo courtesy of Steve McCaw)

Lund University postdoctoral fellow Karin Engström, Ph.D., described her research into the gene-environment interactions involved in arsenic metabolism and toxicity. Her talk was part of the susceptibility to arsenic effects session. (Photo courtesy of Steve McCaw)

Although the formal poster competition was one of the things cancelled because of the weather, the posters were still on display. NIEHS Reproductive Developmental Biology Group biologist Karina Rodriguez, Ph.D., left, and lead researcher Humphrey Yao, Ph.D., took advantage of a break to look at posters. They collaborated with NTP scientists on a study of arsenic and altered mammary gland development, also on display in the session. (Photo courtesy of Steve McCaw)

NTP Neurotoxicology Group postdoctoral fellow Ruben Orihuela, Ph.D., left, described his group's findings. Along with lead researcher Jean Harry, Ph.D., and other members of the group, Orihuela explored the alteration of immune function involved in brain development and repair, triggered by exposure to inorganic arsenic. (Photo courtesy of Steve McCaw)

Following the meeting, Suk, left, enjoyed a talk with Aposhian. In his closing remarks, Suk said about Aposhian, "[His pioneering work with arsenic] is the reason why we are here." (Photo courtesy of Steve McCaw)

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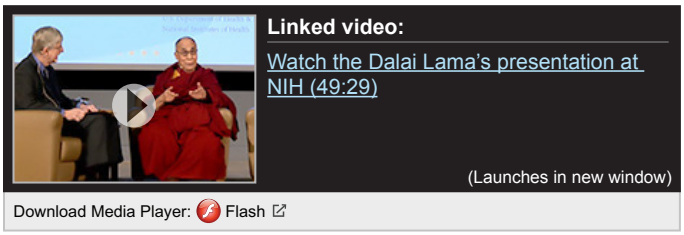
A visit from the Dalai Lama — not an ordinary science talk

By Robin Mackar

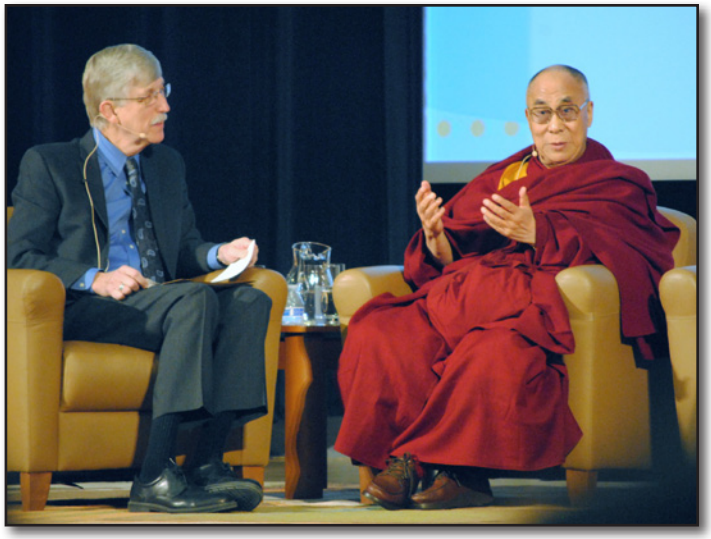
March 7 was an extraordinary day for NIH, as the Tibetan Buddhist Dalai Lama gave a presentation about the role of science in human flourishing, as part of the J. Edward Rall Cultural Lecture series. Some NIEHS staff members were able to attend in person, and others tuned in via webcast.



The Dali Lama took center stage with a smile, a laugh, and an attitude that could warm the soul. (Photo courtesy of Melissa Kerr)

With three large, cozy chairs at center stage in the NIH Natcher Conference Center Ruth L. Kirschstein Auditorium in Bethesda, Md., and a man adorned in a regal red and gold robe, there was every indication that this was not going to be an ordinary science talk.

Tenzin Gyatso, the 14th Dalai Lama and a self-described simple Buddhist monk, is the spiritual leader of the Tibetan people. He received the Nobel Peace Prize in 1989 and has authored or co-authored more than 110 books. Since the 1980s, he has worked with scientists to introduce modern science into the traditional curriculum of Tibetan monastic institutions.



Collins and the Dali Lama discussed the role that science plays in human flourishing. (Photo courtesy of Melissa Kerr)

Science and the mind

After his introduction by NIH Director Francis Collins, M.D., Ph.D., the Dalai Lama received a standing ovation. He bowed to the packed crowd and graciously took the middle seat, with his interpreter at his side. From there it was a freestyle talk, without PowerPoint slides or podium — just a man talking informally about hope, love, the mind, and science.

"I admire science and have a deep respect for it," he said in a quiet voice. "But science alone won't bring inner peace." Genuine peace can only come from love, he added.

"Scientists are very open-minded and objective, and they are full of skepticism and doubt, which is highly necessary for their work." But the Dalai Lama believes that to achieve a deeper level of happiness, scientists can't neglect to develop the inner self.

Reflecting on some of the research he had seen on a tour with Collins prior to the afternoon talk, he referred to these contributions as signs of hope and seemed genuinely touched by the drawings that children at the NIH Children's Inn made for him. He also expressed amazement at the role science could play, mentioning the way advanced technology was helping a 13-year-old girl with cerebral palsy to function better.

Questions from the NIH Director and audience

The talk became a bit more structured when Collins asked the Dalai Lama a few questions, which audience members had submitted ahead of time. After an expansive response to the question of whether science has a role to play in explaining altruism, the Dalai Lama concluded that basic human nature is compassionate and positive.

He stopped, looked at Collins, and said, "I'm ready to argue with you about this," and then gave a contagious laugh that had the audience laughing along with him. Collins smiled and replied, "I love your answer to that and I'm not going to argue."

One of the final questions was a good-humored inquiry about whether the Dalai Lama ever had a bad day or got mad. "Often I lose my temper over small things. Big things, almost never." He told how a reporter once asked him a question about the legacy he wanted to leave. "I'm a Buddhist monk — I want no legacy attached to my name." The reporter wove the same question into her interview two more times. "And on the third time — then I got mad," he said. Collins quickly followed up with a promise to never ask him a question more than once.

The Dalai Lama left all who heard him with a bit more to ponder about how to lead a more peaceful and meaningful life.

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

NIEHS was fortunate to get sought-after tickets to the event. About a dozen employees were able to join NIEHS and NTP Director Linda Birnbaum, Ph.D. for the event in person. Shown standing in line outside the event, from left, are North Carolina Central University student intern Melissa Kerr, Birnbaum, Aubrey Miller, M.D., Kimberly Thigpen Tart, J.D., Bono Sen, Ph.D., and Gloria Galloway. (Photo courtesy of Robin Mackar)

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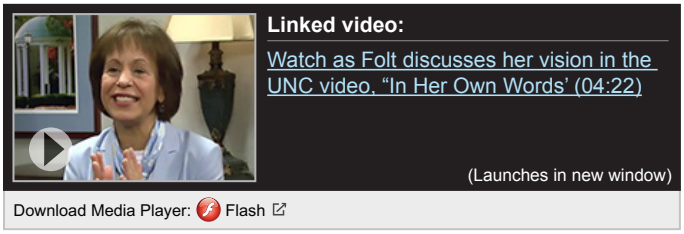
Spirit Lecture features UNC Chancellor Carol Folt

By Eddy Ball

NIEHS welcomed University of North Carolina at Chapel Hill (UNC) Chancellor Carol Folt, Ph.D., March 20 to present the 2014 Spirit Lecture in Rodbell Auditorium.



Folt put the word conversation in the title of her talk for good reason. She was out front interacting with the people in the audience, not standing above them at the podium. (Photo courtesy of Steve McCaw)

Folt's talk, "A Conversation with Carol Folt, Carolina's First Woman Chancellor: From Science to Leadership — Women 'Leaning In,'" described her journey from school girl to woman scientist and leader, encouraging her listeners to embrace challenge, diversity, and change in their lives. She spoke informally as she stood below the podium, facing a capacity crowd that was readily engaged by her infectious enthusiasm, personal charm, and refreshing insight.

Organized by the NIEHS Diversity Council, the Spirit Lecture series began in 2002. Past speakers in the series include NIEHS and NTP Director Linda Birnbaum, Ph.D., who introduced Folt.

"We could hardly ask for a better speaker for this event," Birnbaum said. "Carol had a remarkable career as a scientist, and even got grant money from NIEHS. Now she's leading one of the top universities in the nation. She's everything Spirit Lectures are about."

Birnbaum sat with others in the front row just a few feet away from the speaker. Seated at left is Diversity Council chair Brad Collins, whose video, "Women in History," played as the event got underway. (Photo courtesy of Steve McCaw)

Taking pride in difference

"Women scientists tend to be really good leaders," Folt said as she introduced her concept of True North values. As outsiders, women know that to flourish they need to think big and work hard; embrace difference as an integral part of identity; take risk and learn from failure; and incorporate family values as part of their work.

From her immigrant roots as a third generation Albanian American, Folt said, she learned to see potential, despite what might seem to be insurmountable barriers. "Everything is a 'can,'" she said. And because her life has spanned a time full of fundamental change in every aspect of life, she said, "You always view everything as a moment of something starting."

Even as she encountered intimidating stumbling blocks during her early career in a male-dominated field, Folt remained upbeat and optimistic. She was in the minority during much of this time — the only woman in a 15-member graduate school cohort and one of just five women scientists when she joined Dartmouth College — but she said she often found support from unexpected sources.

From classic ecology to leadership of a flagship university

Folt said her love of water drew her to ecology and the study of lakes. From there it was a natural step to ecosystem toxicology and seeing water as a social justice mechanism. When she began working with Superfund programs at Dartmouth, she discovered a natural fit with her interest in applying science to improve life and solve problems.

She also found a path to collaborative team science, with a multidisciplinary focus that also promoted diversity, creating new opportunities for women and minorities. The transition from Superfund research on toxic metals to applications in children's health was seamless, when Dartmouth established a Children's Environmental Health and Disease Prevention Research Center with funding from NIEHS and the U.S. Environmental Protection Agency.

Almost two decades after joining Dartmouth, Folt found her place as a leader when she was appointed dean of graduate studies and associate dean of the faculty for interdisciplinary programs in 2001. She was named Dartmouth's dean of the faculty in 2004, acting provost in 2009, provost a year later, and interim president in 2012. She took office as UNC's 11th chancellor in July 2013, at a critical point in the flagship university's history.

Looking ahead

"The future rests on big ideas," Folt said as she introduced an impressive catalogue of heroes, role models, and Carolina Firsts, both male and female. They ranged from Dartmouth chemist Karen Wetterhahn, Ph.D., who died of accidental methyl mercury poisoning in the course of her Superfund research, to current compelling thinkers Daphne Koller, Ph.D., Muhammed Yunus, Ph.D., and Bill and Melinda Gates.

"We've still got a long way to go," Folt conceded in response to a question from the audience. But it was clear she is hopeful and confident about the future — for diversity and inclusion, multidisciplinary scientific inquiry, and the evolution of higher education to meet current and emerging challenges.

Not surprisingly, the Spirit Lecture drew many of the Institute's women scientists, such as Environmental Health Perspectives Science Editor Jane Schroeder, D.V.M., Ph.D. (Photo courtesy of Steve McCaw)

Although they were in the minority, several male scientists, including NIEHS Scientific Director Darryl Zeldin, M.D., were on hand for the talk. (Photo courtesy of Steve McCaw)

Contract writer Sara Mishamandani was among several attendees who asked Folt specific questions about the progress of inclusion for women and other minorities in the workforce and within the ranks of leaders and decision-makers. (Photo courtesy of Steve McCaw)

The talk concluded with the traditional presentation of a poster to the guest speaker by members of the NIEHS Diversity Council. Shown from left are Spirit Lecture Committee co-chair Diane Spencer, Folt, Birnbaum, co-chair Veronica Godfrey Robinson, and Collins. Not shown are committee members Eli Ney, Molly Vallant, and Angela King-Herbert, D.V.M. (Photo courtesy of Steve McCaw)

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NIH celebrates equity, diversity, and inclusion

By Kelly Lenox

In what officials promise is much more than a name change, NIH celebrated the new Office of Equity, Diversity, and Inclusion (EDI) with a full schedule of activities March 24-27 (see text box) that included a special flash mentoring session at NIEHS.

Although most of the events were webcast to Research Triangle Park (RTP), N.C. from the NIH campus in Bethesda, Md., NIEHS employees came together to share the celebration kickoff March 24 in Rodbell Auditorium and view the EDI Summit Opening Plenary. As part of the "NIH Women's Symposium 2014 — Looking Back, Moving Forward," they returned to Rodbell Auditorium on Mar. 26 for a videocast of the Women's symposium, and then the "Flash Mentoring Session for NIEHS Scientific and Administrative Staff with Senior Leadership," organized by an NIEHS planning committee chaired by Joan Packenham, Ph.D.

Angela King-Herbert, D.V.M., participated as a mentee, just a week after organizing a flash mentoring and poster session for NTP trainees (see story). (Photo courtesy Steve McCaw)

Underscoring the NIH commitment to EDI

For the past year and a half, beginning with the appointment of Director Debra Chew in 2012, the NIH Office of Equal Opportunity and Diversity Management (OEODM) has been evolving into the new NIH Office of EDI. The strong NIH commitment to excellence in the principles of EDI was evident in comments by speakers in the Opening Plenary, including Director Francis Collins, M.D., Ph.D.

"Our mission will only be effectively accomplished if we establish a creative environment that is equitable and gives everyone the chance to make their contribution in the most productive way," Collins said.

Chew discussed the orientation and goals of the new office. "We are looking to make a paradigm shift, to move past processing complaints of discrimination," she said. "We aspire to a state of equity and fairness within NIH, for all individuals to advance their careers."

Women's concerns, women's empowerment

NIH Women's Symposium 2014 began at NIEHS with a webcast of presentations by nine women in leadership positions at NIH. Deputy Director of NIH Extramural Research Sally Rockey, Ph.D., provided opening remarks. Reviewing her career, Rockey noted an overarching theme. "Embrace the unexpected," she advised the audience.

The morning's agenda featured presentations on the history of women's contributions at NIH, by Stetten Museum curator Michele Lyons, of the Office of NIH History, and an Opening Plenary about the challenges that federally employed women face in the workplace, with a focus on NIH employees.

A breakout session on women and leadership provided the audience an opportunity to question panelists directly. NIEHS Director of Management Joellen Austin responded to a question about traits panelists value when hiring for a leadership position. "I look for evidence the candidate has been willing to take on tough jobs, especially those no one else wants," said Austin, echoing Rockey's earlier advice. She later described moments in her own career trajectory when she took advantage of unexpected opportunity.

Building EDI from a diverse customer base

In the course of re-visioning OEODM into the Office of EDI, staffers underwent a period of intense program evaluation that included customer surveys, focus groups, interviews, and a rigorous examination of the program to better serve its customers; impact civil rights, diversity, and inclusion; and make a lasting difference in the NIH culture and workforce demographics.

To celebrate the launch of EDI, stakeholders involved in building the new Office of EDI participated in a full schedule of events, breakout sessions, and training.

- March 24 — Opening Plenary, breakout sessions, and Resource Group Fair
- March 25 — EDI Training Day, with topics ranging from resume writing, Equal Employment Opportunity for supervisors and employees, and antibullying training
- March 26 — Women's Symposium 2014, honoring Women's History Month, including flash mentoring session
- March 27 — EDI Open House, which gave participants an opportunity to visit EDI offices in Rockville, Md., and on the NIH Campus in Bethesda

Lysandra Castro, biologist in the NTP Molecular Pathogenesis group, was one of more than 30 mentees who registered for the session. (Photo courtesy Steve McCaw)

Flash mentoring

The final event of the day was the flash mentoring session, held in parallel at both NIH and NIEHS. Joan Packenham, Ph.D., introduced the NIEHS session as a series of short, focused conversations around specific questions. Referring to the morning's presentations, Packenham noted that more women than men work at NIH, but not as many hold leadership positions. "A focus on mentoring can help us to address that," she said.

With that, dozens of mentors and mentees began 10-minute conversations, building networks and receiving feedback on questions such as how to find a mentor, how to get to know people beyond one's team or department, and queries specific to each woman's own career. With mentors, both women and men, representing all parts of the Institute, there was an abundance of listening, advice, and new connections made.

Among the 21 mentors participating in the event were Stavros Garantziotis, M.D., front right, Acting Clinical Director, Clinical Research Program; Joan Packenham, Ph.D., center right, Director, Office of Human Research Compliance, and Gwen Collman, Ph.D., back right, director of the Division of Extramural Research and Training. (Photo courtesy Steve McCaw)

Xiaohua Gao, M.D., Ph.D., research fellow in the Molecular Pathogenesis Group, shared a light moment with her mentor. (Photo courtesy Steve McCaw)

In her role as K-12 Science Education & Outreach Coordinator, Hue-Chen Lao is both a mentor to students and, here, a mentee in her own career development. (Photo courtesy of Steve McCaw)

Rodbell Auditorium was vibrant with energy and enthusiasm, such as this congratulatory moment between mentor Matthew Burr, chief of the Administrative Management Branch, and Cathy Jamison, coordinator of the Scholars Connect program. (Photo courtesy Steve McCaw)

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Roundtable explores benefits and challenges of data sharing

By Pamela Kidron

The 13th workshop in the Institute of Medicine (IOM) Roundtable on Environmental Health Sciences, Research, and Medicine series explored the benefits and challenges of sharing environmental health data, and ways to maximize data sharing and satisfy a federal mandate for public access to government data.

The March 19 workshop in Washington, D.C., "Principles and Best Practices for Sharing Data from Environmental Health Research," brought environmental health science researchers together with experts in law and policy.

"The issue [of data sharing] is very complex and is technologically challenging," said NIEHS and NTP Director Linda Birnbaum, Ph.D., who participated in the workshop along with Gwen Collman, Ph.D., director of the NIEHS Division of Extramural Research and Training, and a number of NIEHS grantees.

In 2010, Birnbaum was elected to IOM, one of the highest honors in the fields of medicine and health. (Photo courtesy Steve McCaw)

In a workshop overview, grantee and roundtable vice chair Lynn Goldman, M.D., dean of the George Washington University School of Public Health and Health Services, noted that data sharing is common to many environmental health research studies, which often depend on national survey data, shared data sets, and pooled data.

Over the course of the seven-hour workshop, researchers also highlighted examples of data sharing with the potential for harm. For example, a case was described where shared data sets with demographic information, such as date of birth, gender, and zip code, were linked to a voter registration list, resulting in identification of study participants who had been promised confidentiality.

Identifying benefits and challenges

Several common themes emerged during the roundtable, including the need to strike a balance between protecting confidentiality and making data broadly accessible, and concern that federal regulations could force researchers to make raw research data publicly available.

Participants explored questions such as whether data should be made available to anyone who requests it. Restricting data access to researchers creates the need to establish who is a legitimate researcher and what is a legitimate research question.

Looking Ahead

Another session identified ways to maximize data sharing. For example, one way to address the costs associated with data sharing could be to build those costs into the design of any study or grant request.

Despite concerns, the field of environmental health science generally supports the possibilities and opportunities that broader data sharing brings to its research. Birnbaum noted that data sharing facilitates secondary data analysis and meta-analysis, thus leveraging existing data resources. She also pointed out that data sharing gives access to study findings that have not been published. Also, reanalysis of data with new technologies can improve understanding.

"Once data is published, the raw data upon which it is based should be fully available for others to use — certainly in a collaborative manner — and many times for others to build upon," said Birnbaum. "Reanalysis of data should be done to build upon the original information and ask additional questions, or to look at the data in alternative ways."

Birnbaum explained that NIH is working actively on strategies to encourage and facilitate broader data sharing among researchers in the field of environmental and health science. NIH currently has a number of data-sharing policies, including a requirement that peer-reviewed, published papers funded by NIH be submitted to PubMed Central.

Birnbaum announced at the workshop that upcoming NIEHS data-sharing events include a public webinar April 3 for new and junior researchers to discuss concerns around data sharing, and a June 13 event to identify opportunities for global integration of toxicogenomics databases.

(Pamela Kidron is a contract writer with the NIEHS office in Bethesda, Md.)

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Seminar explores communication of uncertainty and risk

By Kelly Lenox

Objectivity is the touchstone for scientists of every discipline. But when civic responsibility calls for decision making in the context of uncertainty, as it does for scientists in NTP, researchers must grapple with how to effectively communicate their findings.

For insight into how to better express conclusions on potential health concerns associated with exposure to environmental substances, NTP turned to two experts in psychology — David Budescu, Ph.D., of Fordham University, and Thomas Wallsten, Ph.D., of the University of Maryland (UM). Budescu and Wallsten discussed this issue at a seminar March 11 at NIEHS.

For NTP, an important part of reviewing literature-based health assessments (see story) involves examining how to best communicate the results of those assessments, according to Kristina Thayer, Ph.D., director of the NTP Office of Health Assessment and Translation. NTP stakeholders include decision-makers in the public and private sectors, as well as individuals with concerns about their own environmental health.

Budescu is a professor of psychometrics and quantitative psychology at Fordham University. (Photo courtesy of Steve McCaw)

A concern with levels of concern

"When the literature base is well developed, it can result in a formal NTP conclusion referred to as a level of concern (LOC), which integrates what is known about health hazard with the extent of human exposure," Thayer said.

LOC conclusions are narrative rather than quantitative, and that has resulted in some confusion, Thayer continued. "For example, researchers and the public have expressed difficulty in distinguishing between a substance being of 'some concern' and being 'of concern,'" she explained.

Mary Wolfe, Ph.D., director of the NTP Office of Liaison, Policy, and Review, further detailed the challenge of LOC terms. "Do we have too many categories? Should we use numbers along with the words?" she asked. "It's about how we frame the outcome of an evaluation."

Use both verbal and numerical terms

"Decision-makers are best served when the terms used in communicating uncertainty match the ambiguity of the event and the uncertainty of its occurrence," said Budescu (see text box).

As an example of ways to better deal with ambiguity, he pointed to an international study on communicating uncertainty about climate change. In 25 countries, researchers compared the understanding of two forms of conveying uncertainty — verbal terms, and verbal combined with numerical terms. The verbal terms, such as "very likely," were linked to a separate table listing the numerical value of that likelihood.
The verbal combined with numerical terms, such as "very likely (greater than 90 percent probability)," included the numerical value alongside.

Researchers were surprised that, even though a reference table of values was provided, understanding of the verbal terms alone varied considerably among readers. "The presentation of verbal with numerical information achieves better understanding of the terms," Budescu said, noting that understanding improved both across countries surveyed and across all terms used.

Distinguishing sources of uncertainty

Budescu categorized three sources of imprecision when communicating probability.

- The ambiguity of the event itself — for example, "drawing a queen from a deck of cards" is a less ambiguous event than "a drop in the market in the near future."
- The type of uncertainty, or the degree to which the probability of an event can be quantified — for example, "34 percent more likely" is more precisely quantified than "more likely."
- The language of communication — for example, "drop 6 cents per share" is more precise than "drop 10-20 percent in value."

Wallsten is a professor emeritus in the department of psychology and senior scientist at the UM Center for Advanced Study of Language. (Photo courtesy of Steve McCaw)

Obtain and encode expert judgment

Wallsten discussed a process for obtaining and communicating expert judgment — another technique for communicating risk in cases of inadequate data. He outlined an example in which a small panel of 5-7 highly respected scientists was selected using an open and transparent process. The preparation of panel members included enhancing their sensitivity to sources of uncertainty.

The process included numerically encoding the subjective judgments of the expert panel, for example, the likely dose-response rates after exposure to an air pollutant. "Encoding the judgment calls can be useful in representing the extent of consensus or disagreement among the experts," said Wallsten. This step echoed Budescu's finding of the importance of using numerical values when communicating uncertainty.

"Subjectivity cannot be avoided, but it can be translated to a level of concern via an open and principled process," Wallsten concluded.

"We don't use definitions, but, certainly, we can be transparent about how we reached our conclusions," Thayer said of the process of deciding about levels of concern. (Photo courtesy of Steve McCaw)

"We're asking how we can better communicate the outcome of our evaluations," said Wolfe. (Photo courtesy of Steve McCaw)

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Scientists inaugurate inflammation faculty

By Kelly Lenox

Scientists from NIEHS and NTP came together Mar. 11 for the inaugural meeting of the NIEHS inflammation faculty.

Fred Miller, M.D., Ph.D., explained the origin of the group by saying "After the completion of the NIEHS strategic plan, six high priority areas were chosen as areas of focus across the Institute, and inflammation is one of those." Miller, head of the NIEHS Environmental Autoimmunity Group, and Janice Allen, Ph.D., scientific review officer in the NIEHS Division of Extramural Research and Training (DERT), co-led the committee that proposed the new group.

Inflammation is an immune system response that can be normal and restorative, or can result in tissue injury and, ultimately, disease. Diseases that involve inflammation, particularly neurologic, cardiopulmonary, neoplastic, reproductive, metabolic, and autoimmune, are increasing in prevalence and severity, resulting in significant public health costs. Evidence is growing that the environment plays an important role in triggering inflammatory response.

"Inflammation was chosen as one of the priority areas thought to be important in a wide variety of processes and impacting a large number of activities in the Institute," said Allen, who led the meeting. (Photo courtesy of Steve McCaw)

Assessing the state of research

"Through the faculty, we can work together to explore what different groups in the Institute are doing, enhance transdivisional research, and support a workshop of experts from government, academia, and industry to promote research on environmentally-associated inflammation," explained Miller, who participated by conference call from his office in Bethesda, Md.

Allen stressed the cross-divisional nature of the faculty. "With representatives from each division, we are planning for a workshop in spring 2015 to focus on the gaps in knowledge and how best to fill them."

Mike Humble, Ph.D., health scientist administrator in DERT, presented a possible workshop model for the group's consideration, based on his own experience designing and leading an expert panel on autoimmune diseases (see story).

Miller's clinical research group seeks to understand the development of a number of autoimmune diseases characterized by chronic inflammation (Photo courtesy of Steve McCaw).

Humble presented a workshop model he used successfully in the past, for consideration by the faculty as it plans its 2015 workshop. (Photo courtesy of Steve McCaw)

Mike Fessler, M.D., right, head of the Clinical Investigation of Host Defense Group, and Jonathan Hollander, Ph.D., health scientist administrator in DERT, both participated in the kickoff meeting. (Photo courtesy of Steve McCaw)

Following Humble's talk, the group entered into a lively conversation about mission and goal statements. They also discussed a divisional review of activities related to inflammation, a portfolio analysis of current grants on the topic, and hosting talks on current research by NIEHS and other experts. These ideas helped lay the groundwork for upcoming meetings currently planned on a quarterly basis.

Later, Andy Rooney, Ph.D., Deputy Director of the Office of Health Assessment and Translation, emphasized the goal of broad representation in the group. "It is not too late to become part of this," Rooney said. NIEHS and NTP staff should contact a member of the faculty leadership for more information. Allen is principal coordinator, and co-coordinators include Caroline Dilworth, Ph.D., Mike Humble, Ph.D., Fred Miller, M.D., Ph.D., Sri Nadadur, Ph.D., and Andy Rooney, Ph.D.

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Regional symposium addresses reproductive biology

By Shannon Whirledge

Scientists from throughout the Carolinas came together at NIEHS March 8 for the annual meeting of the Triangle Consortium for Reproductive Biology (TCRB). Organized around the theme, "Translating Fundamental Reproductive Sciences," the meeting highlighted research that can lead to solutions for public health concerns.

This year's meeting was the 23rd, but the roots of the consortium go back to 1989. That year John Vandenbergh, Ph.D., professor emeritus at North Carolina State University (NCSU), and the late Clement Markert, Ph.D., also of NCSU, developed the idea for a cooperative effort among reproductive biologists in the Research Triangle region of North Carolina.

Soares is also vice chair for research of the Department of Pathology and Laboratory Medicine, and director of the Division of Cancer and Developmental Biology at the University of Kansas Medical Center. (Photo courtesy of Michael Soares)

Connecting researchers and trainees

Along with keynote and plenary speakers, and 35 abstracts presented in a poster session, this year's meeting continued the tradition of connecting local researchers with students. The experience is a valuable one for trainees, according to Humphrey Yao, Ph.D., head of the NIEHS Reproductive Developmental Biology Group. "We are proud that NIEHS trainees took the opportunity to present their results and receive feedback from their peers," he said. "This experience will prepare them for presentations at formal national and international meetings, as well as job interviews."

The first presentation of the day was by Michael Soares, Ph.D., University Distinguished Professor and director of the Institute for Reproductive Health and Regenerative Medicine at the University of Kansas Medical Center. In his keynote address, "Adaptive Mechanisms Controlling Hemochorial Placentation," Soares discussed the adaptive pathways present during early fetal development, specifically plasticity and placentation.

"The formation of the placenta, which facilitates the delivery of nutrients to the fetus, is central to the early survival of the embryo," he explained. Soares' research group observed that the placenta is formed in response to cues present in the maternal environment, and that faulty adaptive responses during fetal development may lead to long-lasting impacts for health as an adult.

Plenary sessions by regional scientists

In addition to the keynote address, three researchers gave plenary lectures. Wendy Jefferson, Ph.D., shared her work on neonatal estrogen exposure and development of the reproductive tract, in a talk "Early Estrogen Exposure Alters Reproductive Tract Development: Mechanisms and Translation Implications." Jefferson, a biologist in the NIEHS Reproductive Medicine Group, indicated that such exposure can alter global gene expression through locus-specific chromatin modifications, essentially leaving a fingerprint on your DNA.

Maureen Su, M.D., presented her laboratory's research on the autoimmune regulator (AIRE), an important androgen-regulated gene, in her talk, "Mechanisms of Gender Differences in Autoimmunity." Up to10 percent of the population is affected by autoimmune disorders, with a disproportionally higher percentage in women. Su, assistant professor of pediatrics at the University of North Carolina at Chapel Hill (UNC) School of Medicine, speculates that there may be many reasons for these gender differences, including protection by androgens, a class of male hormones. Her research incorporated a multiple sclerosis model, where AIRE induction by androgens diminished disease severity.

The final plenary, presented by Bruce Lessey, M.D., Ph.D., addressed endometriosis, a disease affecting roughly 176 million women, worldwide, and costing the U.S. over $22 billion dollars per year. Approximately 30-50 percent of patients with endometriosis are infertile. Lessey, clinical professor in the University of South Carolina School of Medicine Greenville Department of Obstetrics and Gynecology, stressed the need for better diagnostic tools and improved surgical interventions.

Postdoctoral researchers present posters

In addition to the invited speakers, four of the poster session's 35 abstracts were chosen for oral presentation. NIEHS postdoctoral fellows gave three of the four oral presentations. Also, for the first time, the Campion Fund, supported by the Phyllis and Mark Leppert Foundation for Fertility Research, (see text box), provided awards for best oral presentation and best poster presentation to two junior investigators. In the inaugural year of this award, both recipients were from NIEHS (see story).

Fellowship support

The Campion Fund recognizes the need to support and fund scientists studying human reproductive diseases. The Phyllis and Mark Leppert Foundation, a 501 (c) (3) public charity, was founded to promote basic biomedical research in this area, and the Campion Fund supports research through tax-deductible donations to the Foundation. In addition to funding scientists through the Campion Fund, the Leppert Foundation works to provide education regarding fertility research to the public and will host an annual conference for the scientific community.

Jefferson is a senior member of the NIEHS Reproductive Medicine Group headed by Carmen Williams, M.D., Ph.D. (Photo courtesy of Steve McCaw)

Su is also affiliated with the Inflammatory Disease Institute, Lineberger Cancer Center, and Center for Environmental Medicine, Asthma, and Lung Biology at UNC. (Photo courtesy of Maureen Su)

In addition to his academic appointment, Lessey practices reproductive endocrinology as part of the Greenville [S.C.] Health System. (Photo courtesy of Bruce Lessey)

(Shannon Whirledge, Ph.D., is an Intramural Research Training Award fellow in the NIEHS Laboratory of Signal Transduction.)

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Trainees shine at reproductive biology symposium

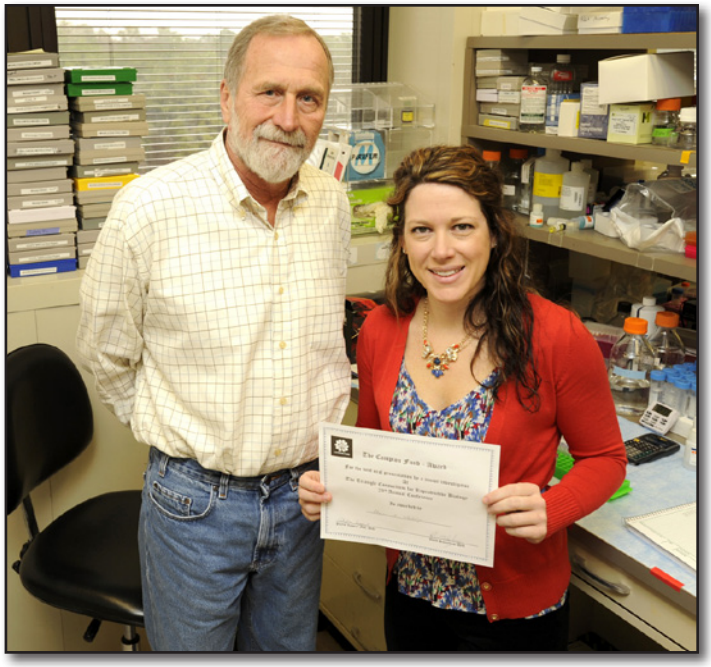
By Deepa Singh

Two NIEHS trainees received recognition at a symposium March 8 in Research Triangle Park, N.C., winning top awards for their presentations during the 23rd annual meeting of the North Carolina Triangle Consortium for Reproductive Biology (TCRB). The awards include cash prizes of $2500 from the Campion Fund.

Shannon Whirledge, Ph.D., an Intramural Research Training Award fellow in the Laboratory of Signal Transduction (LST), won for best oral presentation in competition with two other NIEHS trainees and a trainee from the East Carolina University Brody School of Medicine. A poster presentation by Chang Liu, a predoctoral fellow in the Laboratory of Reproductive and Developmental Toxicology (LRDT), received top honors in the competition that included 35 posters.

Award winners Liu, left, and Whirledge had reason to smile about their awards and the substantial cash prize involved. Their honors reflect the rigorous training in written and oral presentation skills, as well as critiques they've received from colleagues in LRDT and LST. (Photo courtesy of Steve McCaw)

TCRB is a thriving organization that brings together scientists focusing on reproductive biology from leading biomedical research organizations and has more than 200 members, representing 18 institutions from throughout North Carolina. The symposium was sponsored by NIEHS and the Leppert Foundation, whose goal is to provide and sponsor research that will lead to healthier lives, pregnancies, and birth (see story).



Cidlowski, left, hosted Whirledge's presentation on her research at the Feb. 4 meeting of the NIEHS Receptor Mechanisms Group. (Photo courtesy of Steve McCaw)

Shannon Whirledge

Whirledge, a graduate of the Baylor College of Medicine, joined the Molecular Endocrinology Group headed by John Cidlowski, Ph.D., in 2009. The focus of her work at NIEHS is the glucocorticoid receptor (GR) signaling in the uterus. In addition to her Campion award, Whirledge has received honors from the Endocrine Society and the Society for the Study of Reproduction (SSR). Her 2012 study on GR signaling and uterine fibroids received special recognition from the journal Hormones and Cancer (see story).

"John has been incredibly supportive of this project since I came to NIEHS in 2009," Whirledge said of her mentor. "He is very excited about evaluating the role of glucocorticoid receptors throughout the body, especially the link between glucocorticoid receptor signaling and fertility. He believes stress and fertility will provide a basis for my career as an independent researcher."

"In addition to the support from my own lab, the LRDT groups have given me a wealth of knowledge and technical support," Whirledge continued, "in particular Dr. Kenneth Korach's group, Dr. Carmen Williams, and Dr. Humphrey Yao."

Award-winning research

- Whirledge's oral presentation — "Uterine Glucocorticoid Receptor Knockout Mice Are Subfertile and Have Aberrant Signal Transduction"

  This work demonstrated for the first time that the glucocorticoid receptor can profoundly affect uterine functions by direct action on the uterus itself and not through the brain's hypothalamic-pituitary-gonadal axis alone. These results suggest that the glucocorticoid receptor regulates uterine biology and fertility through uterine-specific actions.

- Liu's poster presentation — "Somatic Cell Linage Establishment During Organogenesis of the Mouse Ovary"

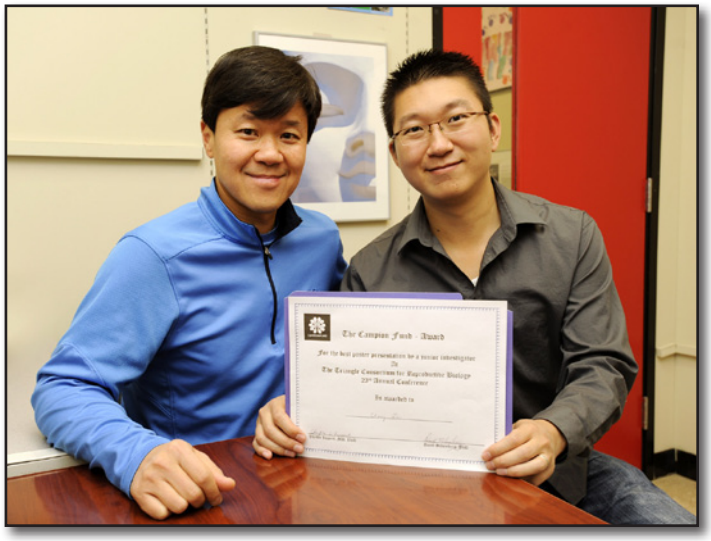
  Despite the functional importance of theca cells in follicle development, very little is known about their origin and process of differentiation. Liu's work provides clear evidence that the theca cells of the ovary have two origins during development — the gonadal somatic progenitor cells and the mesonephros. Understanding the origin of these cells in the developing fetus assists in the understanding of the normal process of development and how diseases such as infertility and ovarian cancer may arise.

Chang Liu

Liu joined the Reproductive Developmental Biology Group headed by Humphrey Yao, Ph.D., in 2009 as a visiting predoctoral fellow after completing a master's degree at the University of Illinois (UI) at Urbana-Champaign. Liu's award-winning work investigated cell lineage establishment during organogenesis using mouse models and how defects in this process affects fertility.

Liu also won the Lalor Foundation Merit Award and the SSR Trainee Research Award at the SSR meeting in September 2013 in Montreal (see story). He credits the success at both meetings to the training experience he is receiving at NIEHS.

"NIEHS has a lot of resources for research so that I can apply whatever is needed to answer important questions," Liu said of his fellowship experience. "I feel very lucky to have Humphrey Yao as my mentor, who has put a lot of effort into training and preparing me for an academic career."



Liu's relationship with Yao began at UI, where Yao was an associate professor prior to joining NIEHS. "There are things I've learned from him that I think will be beneficial for the rest of my life," Liu said. (Photo courtesy of Steve McCaw)

For Yao and Cidlowski, the TCRB symposium is a great place for students and professors in the Triangle area to exchange ideas and present their exciting work, and it also encourages collaborations. The format of the meeting this year was different, because it offered fellowships for the first time that supported awards for trainees.

(Deepa Singh, Ph.D., is a visiting fellow in the NIEHS Mechanisms of Mutation Group.)

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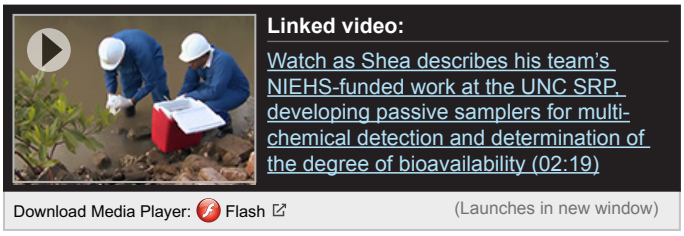
UNC Superfund scientists study effects of Dan River coal ash spill

By Sarah Yelton

One of the largest coal ash spills in the nation's history began Feb. 2 in Eden, N.C., at a Duke Energy containment pond on the banks of the Dan River. According to a U.S. Environmental Protection Agency (EPA) estimate, by the time the discharge was stopped, 50,000 to 80,000 tons of toxic coal ash had entered the Dan River, lining its banks and depositing waste along the riverbed for 70 miles downstream.

In response to this environmental challenge, a team of NIEHS-funded scientists led by Damian Shea, Ph.D., joined forces with state and federal regulatory agencies, to help answer important questions about the toxic chemicals present in the coal ash. The information from the team's research should enable regulators to better assess potential risks to human health in communities along the river.



Shea is a University of North Carolina at Chapel Hill (UNC) Superfund Research Program (SRP) researcher and a professor of biological sciences at North Carolina State University (NCSU).

"Our goal is to help our agency partners determine exactly what toxic chemicals are present in this coal ash, as well as to what extent these chemicals are present in water and sediment in the river," Shea explained. "There are a number of potentially hazardous chemicals contained in coal ash, primarily toxic metals, such as arsenic and selenium. Cancer-causing chemicals, including polycyclic aromatic hydrocarbons (PAHs), may also be present at lower levels."

U.S. Fish and Wildlife Service and Duke Energy crews prepare to take water quality samples in the Dan River. (Photo courtesy of the U.S. Environmental Protection Agency)

What chemicals are present?

Shea and his lab team at NCSU are currently working with the U.S. Fish and Wildlife Service, EPA, N.C. Department of Environment and Natural Resources, and N.C. Department of Health and Human Services to collect and properly store samples of coal ash, water, bottom sediments, and organisms such as fish and mussels from a number of sites along the river, for lab analysis.

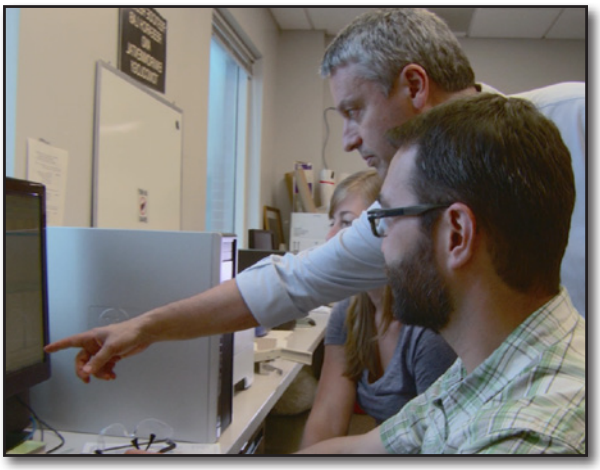
"There is limited information on how quickly the metals and other chemicals are released from the coal ash to enter the water and food chain," Shea said. Using ash from the containment pond, Shea and his team will conduct experiments to determine how quickly metals, PAHs, and other chemicals are able to enter the water column.

Coal ash was deposited on the banks of the Dan River, just downstream of the spill location. (Photo courtesy of the U.S. Environmental Protection Agency)

Evaluating the potential for exposure

With passive sampling devices that remain in the river for 30-day intervals, Shea and his team are assessing the type and amount of chemicals people may be exposed to over the long term, as well as the percentage of those chemicals that are bioavailable, or absorbed by an organism.

"One of the goals of our program is to apply university resources to help governments and the public make informed decisions about reducing risk from hazardous chemicals," said Kathleen Gray, one of Shea's SRP colleagues and leader of the UNC SRP Research Translation Core. "Damian's sampling and analysis is serving a critical need for information on how this contamination may affect health in the future."



Shea, standing, and the team analyze samples in the lab. (Photo courtesy of the UNC SRP)

(Sarah Yelton is an environmental education coordinator with the Environmental Resource Program at UNC and UNC SRP Research Translation Core leader.)

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Building global partnerships to improve research communication

By Audrey Pinto

In March, Banalata (Bono) Sen, PhD., program coordinator for the NIEHS Global Environmental Health (GEH) program, made good on the Institute's long-standing commitment to international collaborations. In response to an invitation from the Public Health Foundation of India (PHFI), one of India's premier public health institutions, Sen conducted a workshop on research writing and publishing in peer-reviewed journals.

Sen's course was part of a two-week professional development workshop in New Delhi, funded by a Wellcome Trust training and capacity building grant and sponsored by the London School of Hygiene and Tropical Medicine (LSHTM). Twenty junior faculty members and postdoctoral candidates at PHFI participated in Sen's three-day seminar.

Leading the workshop was a natural fit for Sen, who has long worked to establish partnerships with public health agencies overseas. (Photo courtesy Arushi Chandra of PHFI)

Helping scientists from developing countries publish innovative research

Teaching the workshop was a logical move for Sen, who has long advocated for partnerships, education, training, and outreach for researchers and scientists from low-income and middle-income countries (LMIC). She developed the workshop while working for the NIEHS journal Environmental Health Perspectives (EHP).

Sen's passion was evident, as she described the workshop's origin. "While working at EHP, I saw innovative research being rejected because the researchers did not understand how to target their written findings for a specific journal," she explained. "My workshop evolved out of the need to raise awareness of the peer-review publishing process, so that scientists from LMICs could create a successful product."

The response to Sen's workshop was enthusiastic. "Bono's workshop was extremely illuminating — her friendly, interactive, and responsive style of instruction suited the audience very well, and the content of the workshop was varied and interesting," said one of the organizers, LSHTM epidemiologist Pat Doyle, Ph.D. "The participants especially valued the practical sessions that combined technical aspects of scientific writing with understanding the complete process of writing for publication."

Nurturing collaborations with public health organizations in LMICs

"Scientists from LMICs do not receive the same type of training, nor do they have access to the wealth of resources available to students and researchers from developed countries," said Sen. Along with language issues, these deficits can hamper publication of unique scientific findings and limit opportunities for collaborations within the global community of researchers.

"This workshop and partnership with PHFI started when I was working as the program manager for education and outreach for EHP," explained Sen. "Although my relationship with PHFI started at that time, the collaboration dovetailed very nicely with my current role as program coordinator of GEH, and as lead coordinator for training and capacity building for the NIEHS World Health Organization (WHO) Collaborating Centre for Environmental Health Sciences."

Recognizing that environmental health problems cross national and international borders, NIEHS identified global environmental health as an integral component of its 2012–2017 Strategic Plan and established the GEH program in 2013.

(Audrey Pinto, Ph.D., is technical editor for the journal Environmental Health Perspectives.)

The junior faculty and postdoctoral students enrolled in the workshop responded enthusiastically to Sen's course. (Photo courtesy Arushi Chandra of PHFI)

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Collaboration, focus, and innovation keys to replacing animal use

By Catherine Sprankle

Warren Casey, Ph.D., director of the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), delivered the keynote address at a Feb. 27 gathering of researchers and regulators in Somerset, N.J.

The 3Rs Sharing Conference, "Paving the Path to Regulatory Acceptance of Alternative Methods: Facilitating the Integration of Alternative Methods Into the Regulatory Framework," included speakers from the pharmaceutical and chemical industries presenting case studies and strategies for effective safety testing using fewer animals. The New Jersey Association for Biomedical Research (NJABR) sponsors the annual conference

NJABR

NJABR organizes annual 3Rs Sharing Conferences at which veterinarians, toxicologists, members of animal welfare organizations, and others come together to discuss best practices to replace, reduce, and refine animal use for biomedical research and safety testing.

NJABR is part of a loose national network of organizations that advocate for the continued availability of animal models for biomedical research.

Casey noted that increasing NTP leadership and direction for ICCVAM will better support the acceptance and use of testing methods that reduce or replace animals. (Photo courtesy of Thomas Leach, New Jersey Association for Biomedical Research)

Evolution of NTP and interagency alternative methods programs

Casey's keynote, "New Direction and Transformation of NICEATM and ICCVAM," addressed recent changes in NICEATM and the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), which NICEATM supports. He outlined how these changes will allow ICCVAM to use limited resources more effectively, leverage the efforts of international partners, and take advantage of innovations in toxicological science.

He also discussed ICCVAM's advisory role and emphasized that collaboration and coordination will be important to future success. "Considering ICCVAM's limited resources, the projects the committee takes on need to be those most likely to lead to real reductions in animal use, in areas such as vaccine testing, acute toxicity testing, and identification of skin sensitizers," Casey noted. "But if ICCVAM collaborates and communicates effectively with its international partners and other stakeholders, the efforts of those partners can support ICCVAM's progress towards its goals."

In the past, NICEATM focused primarily on providing support to ICCVAM. Recently, NICEATM became active in the interagency Tox21 collaboration, of which NTP is a partner. "NICEATM's expertise in validation study design and data analysis will help Tox21 achieve its goals of developing predictive toxicological models and reducing reliance on animal testing," said Casey.

(Catherine Sprankle is a communications specialist for Integrated Laboratory Systems Inc., the contractor supporting NICEATM.)

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Duke and UNC SRP scientists connect with journalists

By Megan Avakian

To help the public better understand the real-world applications of their research, the NIEHS-funded Duke University and University of North Carolina at Chapel Hill (UNC) Superfund Research Program (SRP) Research Translation Cores (RTC) co-hosted a workshop March 5-6, focused on communicating science to the media. Eighteen journalists from national and local news outlets interacted with RTC scientists to learn about SRP issues and how they are relevant in people's everyday lives.

Meeting face-to-face with Duke and UNC SRP scientists allowed the journalists to connect to the research on a personal level. "The workshop helped to raise the journalists' awareness of the SRP and allowed them to see it as a very relevant area of scientific research," said Kathleen Gray, leader of the UNC RTC.

The workshop was part of a weeklong learning expedition sponsored by the Institutes for Journalism and Natural Resources (IJNR), which provides fellowships to journalists, to meet with scientists in the field and in laboratories, to learn firsthand about environmental issues. Duke and UNC RTC staff helped plan the agenda, which focused on issues of environmental contamination.

Drew Cade, Lake Crabtree County Park manager, discussed community impacts downstream of the Ward Transformer Superfund site with visiting journalists. (Photo courtesy of Sarah Yelton of UNC)

Workshop highlights

Field activities on the first day began with a visit to the Ward Transformer Superfund site, where the IJNR fellows learned about the site's history, polychlorinated biphenyl (PCB) contamination in soil and fish, and downstream contamination. According to Gray, the journalists were interested in the fish consumption advisories associated with the Ward site and whether they were effective for informing and protecting the public from PCB contamination.

Journalists learned about the history of PCB contamination and remediation at the Ward Transformer Superfund site in Raleigh, N.C., from U.S. Environmental Protection Agency staff and contractors. (Photo courtesy of Sarah Yelton of UNC)

The group then traveled to the Duke campus, where several SRP researchers, including Richard Di Giulio, Ph.D., director of the Duke SRP, and James Swenberg, D.V.M., Ph.D., director of UNC SRP, provided an overview of the research being conducted at each of the centers.

Duke SRP environmental chemist Heather Stapleton, Ph.D., gave the fellows a tour of her lab and explained her research on brominated flame retardants in foam furniture cushions. Stapleton also allowed the journalists to submit foam samples from furniture in their homes and workplaces for analysis.

UNC SRP molecular biologist Rebecca Fry, Ph.D., also spoke to the group about her research on how arsenic and cadmium affect human health.

The day closed with a presentation from Heather Henry, Ph.D., NIEHS SRP health science administrator, about online tools and resources journalists can use to learn more about SRP, environmental chemicals, and exposures.

The next morning, the fellows heard from UNC epidemiologists Steve Wing, Ph.D., and Ginger Guidry, Ph.D., about the range of environmental chemicals people are exposed to in their daily lives.

Representatives from the local environmental advocacy groups ToxicFree NC and Neuse Riverkeeper Foundation also spoke about the role of policy to protect human health and the environment.

Raising awareness and building connections

The workshop increased the journalists' general awareness of SRP-funded research and Superfund contaminants, connecting some participants to the issues for the first time and giving others new story angles. Several of the journalists signed up to receive the centers' newsletters, to stay current with Duke and UNC SRP research and activities.

Another valuable outcome of the workshop was the bidirectional communication network that was established between the journalists and scientists. "Now our centers have connections to environmental reporters who can translate and share our research with wider audiences," said Charlotte Clark, Ph.D., leader of the Duke RTC.

"The journalists stressed how important it is to have access to scientists who can verify information from multiple, and sometimes conflicting, online sources," Henry added.

(Megan Avakian is a research and communication specialist for MDB Inc., a contractor for the NIEHS Superfund Research Program and Division of Extramural Research and Training.)

Fry shared her research on the health effects of exposure to arsenic with IJNR fellows. (Photo courtesy of Sarah Yelton of UNC)

Swenberg provided journalists with an overview of the mission and research projects of the UNC SRP. (Photo courtesy of Sarah Yelton of UNC)

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NTP holds flash mentoring session for trainees

By Eddy Ball

NTP caught a flash wave that's been sweeping NIH recently, with a mentoring and poster session for trainees March 20 in the NIEHS Rodbell Auditorium. Ten senior scientists and ten trainees, ranging from predoctoral fellows to research fellows, attended the event, which was moderated by Suzanne Fenton, Ph.D., head of the Reproductive Endocrinology Group in the NTP Laboratory.

Flash mentoring refers to a rapid-fire verbal interchange, typically around five or six minutes in length, between a senior figure, or mentor, — in the case of NIEHS and NTP, a lead scientist or program manager — and a less experienced individual, typically a trainee, job seeker, or aspiring employee. The mentor and trainee discuss career development issues, in a situation that's been described as similar to speed dating, with mentees rotating to different people every few minutes.

The exercise, which is often used by businesses to meet new customers, helps participants learn to think quickly and network effectively, in about the same amount of time available during refreshment breaks at meetings and symposia. This flash mentoring sessions was especially timely, because several of the trainees were on their way to the annual meeting of the Society of Toxicology.

In the case of the NTP event, it also gave staff housed in separate buildings a chance to learn more about the various offices, branches, and labs in the Division of NTP (DNTP) and interact with people they may not have met or talked with before. "This was a great way to bring everyone together," Fenton said afterwards.

Building cohesion and esprit de corps

"Like a well-developed thunderstorm, it'll be over before you know it," Fenton told participants in her opening remarks. She warned them that the stopwatch on the screen at the front of the room would keep ticking to signal when to move from one station to the next. Participants had 5 ½ minutes to talk, with 30 seconds allowed for moving to the next flash interaction.

The room quickly came to life with the buzz of ten conversations happening simultaneously. Typically, mentors described their work and the sometimes-unexpected developments in their own career paths. Trainees discussed their work in NTP programs, their goals, and their career concerns.

Several trainees made new friends and potentially important contacts. "Stop by any time and talk," said Darlene Dixon, D.V.M., Ph.D., lead of the Molecular Pathogenesis Group in the NTP Laboratory, to several of the young people who met with her.

Participants

NTP Mentors

- Warren Casey, Ph.D. — NTP Interagency Center for the Evaluation of Alternative Toxicological Methods
- Mike Devito, Ph.D. — Toxicology Branch
- Darlene Dixon, D.V.M., Ph.D. — NTP Laboratory
- Michelle Hooth, Ph.D. — Program Operations Branch
- Ruth Lunn, Dr.PH. — Office of the Report on Carcinogens
- Dave Malarkey, D.V.M., Ph.D. — Cellular and Molecular Pathology Branch
- Scott Masten, Ph.D. — Office of Nominations and Selection
- Andy Rooney, Ph.D. — Office of Health Assessment and Translation
- Ray Tice, Ph.D. — Biomolecular Screening Branch
- Nigel Walker, Ph.D. — NTP Associate Director's Office

NTP Trainees

- Sheba Churchill, D.V.M. — Laboratory Animal Management Group
- Adam Filgo — Reproductive Endocrinology Group
- Madisa Macon, Ph,D, — Reproductive Endocrinology Group
- Deirdre Robinson — Reproductive Endocrinology Group
- Xiaohua Gao, M.D., Ph.D. — Molecular Pathogenesis Group
- Rachel Goldsmith, Ph.D. — WormTox Group
- Jui-Hua Hsieh, Ph.D. — Molecular Toxicology and Informatics Group
- Tanasa Osborne, D.V.M., Ph.D. — NTP Pathology Group
- Katie Pelch, Ph.D. — Inorganic Toxicology Group
- In Ok Surh, Ph.D. — General Toxicology Group

"We needed this," Fenton said of the experience. "This was awesome." Although she could not be present, because she was giving an invited lecture, Angela King-Herbert, D.V.M., led the planning of this event, along with Dixon, Fenton, and Michelle Hooth, Ph.D.

Although Churchill, above, had seen Walker at meetings and talks, she'd never had occasion to have his full attention for a five-minute conversation, before she landed at his station during the flash mentoring session. (Photo courtesy of Steve McCaw)

Tice was clearly enjoying his flash conversation with Goldsmith, proving that business and fun can readily mix. One of Tice's recommendations could apply to anyone — trainee or senior scientist. "You need to broaden your horizons," he said. (Photo courtesy of Steve McCaw)

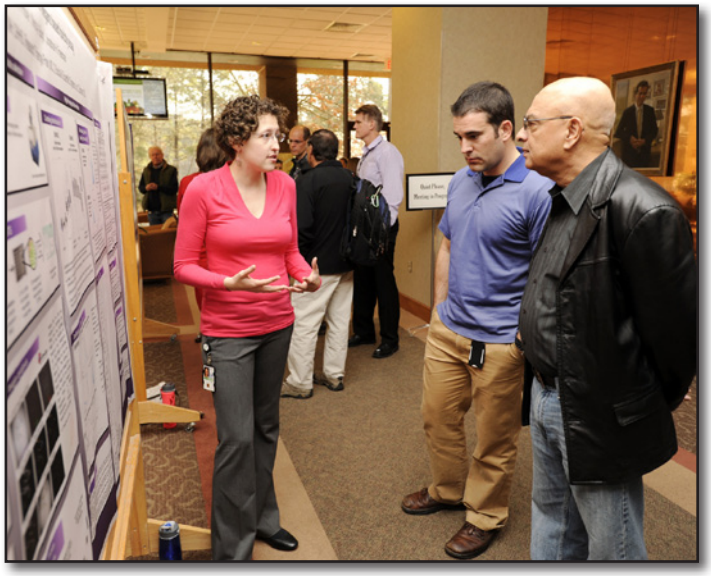
During one of his first stops, predoctoral trainee Filgo quizzed Lunn about the Report on Carcinogens, a high-profile publication NTP produces every two years for the Secretary of the U.S. Department of Health and Human Services. (Photo courtesy of Steve McCaw)

Hooth offered insights about networking during her talk with Filgo. They seemed to agree that flash mentoring is an idea whose time has come, in science, as well as business. (Photo courtesy of Steve McCaw)

Fenton devoted most of her attention to monitoring the time, but she jumped in toward the end when trainees ran out of new mentors to visit. She is shown talking with Surh about her own career path, which took her from the U.S. Environmental Protection Agency to NIEHS and NTP in 2009. (Photo courtesy of Steve McCaw)

During the poster session, Robinson, right, described her research to Dixon. Robinson has studied altered mammary development in mice following inorganic arsenic exposure. (Photo courtesy of Steve McCaw)

As Filgo listened, Pelch, left, explained the complicated methodology in her study of DNA methylation changes following metal exposure in prostate cells. (Photo courtesy of Steve McCaw)



From left, Goldsmith talked about her analysis of high-throughput, high-content data in a C. elegans model, with NTP fellow Brian Sayers, Ph.D., and NTP Postdoctoral Training Program Coordinator Raj Chhabra, B.V.Sc. (D.V.M. equivalent), Ph.D. (Photo courtesy of Steve McCaw)

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Science Notebook

Distinguished lecture highlights RNA discoveries

By Ernie Hood

Remarkable new insights about RNA cellular mechanisms took center stage at the March 11 NIEHS Distinguished Lecture Series talk by Melissa Moore, Ph.D. The lecture, "Assembly and Dynamics of Uber Complex RNPs," was hosted by Karen Adelman, Ph.D., head of the NIEHS Transcriptional Responses to the Environment Group.

Adelman, who organized and hosted the event, said of Moore, "She's been a hero of mine since I first met her nine years ago. Her lab works on the questions she addresses in many different ways. They do everything from single-molecule biophysics, to looking at some of the causes of neurodegeneration." (Photo courtesy of Steve McCaw)

Moore is a professor of biochemistry and molecular pharmacology and co-director of both the RNA Therapeutics Institute and the Neurotherapeutics Institute at the University of Massachusetts Medical School (UMMS). She is also a Howard Hughes Medical Institute investigator. Moore's lab focuses on eukaryotic RNA processing and metabolism.

In her lecture, Moore described important discoveries that shed new light on how RNA is transported at the cellular level, and the diseases that can result when the process goes awry.

A budding phenomenon

RNA is made in the nucleus of the cell, but to become translated into proteins, it needs to move into the cytoplasm, where the machinery for translation resides. It had long been assumed that the only way for that to happen was for RNA complexes to squeeze, one by one, through tiny holes in the membrane surrounding the nucleus, known as nuclear pore complexes.

A collaborative effort between Moore and the lab of Vivian Budnik, Ph.D., also at UMMS, resulted in discovery of a novel mode of transport in which large packages of RNA, called ribonucleoprotein complexes (RNPs), exit the nucleus by budding directly through the nuclear membrane.

"The bottom line for this story is that the nuclear pore is not the only way out of the nucleus," Moore explained. "There is another pathway."

Moore's zest for science was evident throughout her lecture. For example, she told her listeners, "I have a basic theory — if I can think of it, biology's done it, and biology can do a lot more things than I can think of." (Photo courtesy of Steve McCaw)

Moore said that the budding transport mechanism has been documented in many eukaryotic cell types, including yeast and human cells, such as neurons. “Once you know what you’re looking for, you can see these things everywhere,” she said. “We do believe it is a universal process.”

Multiple proteins are involved in budding, and mutations in any of them can disturb this process. Such mutations are associated with genetic diseases such as progeria, the condition characterized by premature aging, and dystonia, a neurological movement disorder.

“The budding process is clearly linked to multiple human diseases whose mechanistic basis was not previously understood,” Moore noted.

Moore’s talk attracted a wide-ranging audience, including neurobiologists such as David Armstrong, Ph.D., right, head of the Membrane Signaling Group, and structural biologists, such as Thomas Kunkel, Ph.D., lead researcher of the DNA Replication Fidelity Group.

A new way to visualize RNAs

The second section of Moore’s talk dealt with her lab’s work characterizing the structure of large RNA complexes, such as exon junction complexes (EJCs) and messenger RNPs (mRNPs).

Until now, scientists thought of messenger RNA (mRNA) as a free-floating, single-strand string in the cell, with various proteins binding along the strand, known as the beads on a string model. Looking at a specific complex bound onto mRNA, Moore instead found that the protein complexes appear to aggregate with the RNA to form more complex, tightly bound structures in which the proteins interact with each other, as well as with the RNA itself. This helps the RNA fold up. So, instead of being a linear molecule in the cell, it is actually a globular complex.

Lecture attendees learned about discovery of a novel mode of RNA transport in the cell, and a new way to visualize RNA complexes. (Photo courtesy of Steve McCaw)

According to Moore, the structure of the complex can alter how other molecules interact with it, and whether certain portions are accessible on the surface or are buried below the surface. In theory, this folding serves to protect the RNA from the many enzymes in the cell that could degrade naked RNA, or RNA with no proteins bound to it.

Moore noted that there are now more than 1,000 different proteins known to interact with mRNAs, a sign that posttranscriptional regulation of gene expression is just as complicated as pretranscriptional regulation. Large RNA complexes, such as EJCs and mRNPs, contribute to RNA localization, a widespread mechanism for posttranslational gene regulation.

(Ernie Hood is a contract writer with the NIEHS Office of Communications and Public Liaison.)

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Cholesterol gene may be responsible for increased inflammation

By Robin Arnette

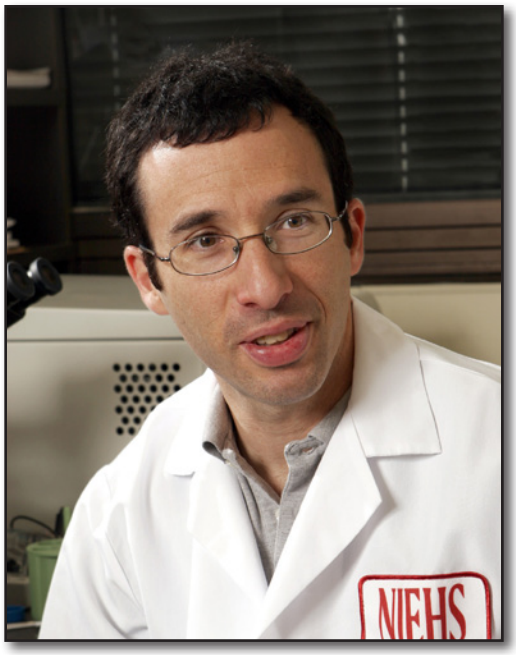
People with a certain form of the cholesterol-controlling gene apolipoprotein E (APOE) may be more prone to inflammation than others, according to a new NIEHS study.

The APOE gene helps to regulate and distribute cholesterol and other lipids in the body. It exists in three forms, or alleles — APOE2, APOE3, and APOE4. The APOE3 allele maintains the proper cholesterol-removing function of the gene. NIEHS researchers and their collaborators were the first to report that people who have APOE4, which does not effectively remove lipids, experience much more robust inflammatory response. They published their results online March 20 in the Journal of Allergy and Clinical Immunology.

Michael Fessler, M.D., an NIEHS researcher and corresponding author on the paper, said that APOE4 has been associated with inflammatory conditions, such as heart disease and Alzheimer's disease, and that 15-20 percent of the human population has the APOE4 allele.

He noted that doctors can't yet tailor therapy for a patient based on whether they have APOE4, but it may be feasible soon. In early clinical trials, researchers are using peptides that mimic APOE3 to treat a variety of human diseases, including brain disorders and heart disease. Peptides are small proteins with fewer than 50 amino acids.

"These peptides have been shown to be anti-inflammatory," Fessler said, "so it's possible, but not proven, that these APOE peptides could be used in patients — perhaps in patients with APOE4 specifically — to reduce their risk of developing inflammatory diseases."

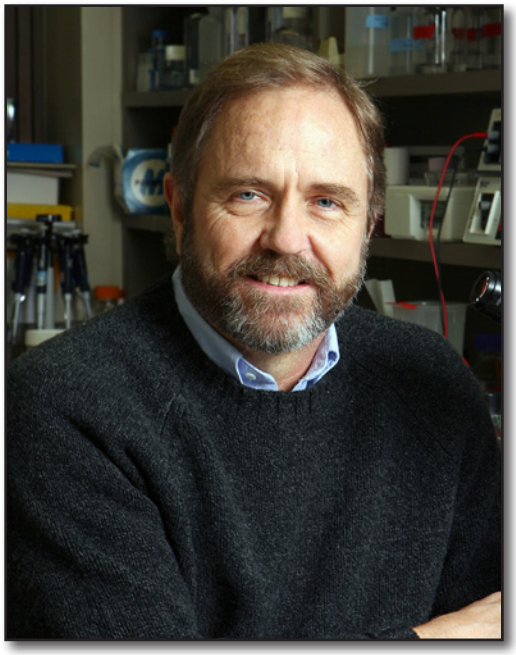


Fessler noted that the NIEHS Clinical Research Unit played a major role in this work. "It was great having the EPR as resource," he said. "We wouldn't have been able to do our study without it." (Photo courtesy of Steve McCaw)

All data point to one outcome

The team examined APOE4 and its effects four different ways. First, the researchers used blood samples from the NIEHS Environmental Polymorphisms Registry (EPR), a long-term research project to collect and store DNA from approximately 20,000 North Carolinians. Team members placed samples in test tubes and added lipopolysaccharide (LPS), the major component of the outer surface of bacteria. The researchers found that blood from volunteers with at least one copy of APOE4 produced a more robust inflammatory response to LPS than those with two copies of APOE3.

They saw the same result when they gave another group of volunteers LPS intravenously. People with APOE4 exhibited a higher fever response and more inflammatory proteins in their blood. Next, the team gave LPS to mice genetically engineered to express human APOE4. The mice exhibited a similar enhanced response.



Blackshear heads the Post-translational Gene Expression Group in the NIEHS Laboratory of Signal Transduction. (Photo courtesy of Steve McCaw)

Lastly, the researchers studied more than 800 sepsis patients. Sepsis, an unregulated inflammatory response to infection, results in low blood pressure and is life threatening. Again, patients with one copy of APOE4 exhibited a more intense inflammatory response.

Each segment of the study confirmed APOE4 as a factor that increases inflammation. "This is a good example of first applying basic research findings to a clinical problem, and then returning to the lab to explore the mechanisms of the clinical effect," said co-author and NIEHS researcher Perry Blackshear, M.D., D.Phil.

APOE4 and other illnesses

Fessler said future work will investigate whether APOE4 can contribute to additional common inflammatory diseases. He added that scientists have found variations in other genes that may affect inflammation in humans, but in most cases, these variations have not been demonstrated using cells from patients.

Fessler is glad that his work has added APOE4 to the list of genetic determinants of inflammatory risk in humans. He believes the collective outcome of future studies will shape the next wave of medicine. "With this information, physicians could one day customize or tailor prognoses and treatment based on a panel of genetic and environmental risk factors," Fessler said.

Citation: Gale SC, Gao L, Mikacenic C, Coyle SM, Rafaels N, Murray T, Madenspacher JH, Draper DW, Ge W, Aloor JJ, Azzam KM, Lai L, Blackshear PJ, Calvano SE, Barnes KC, Lowry SF, Corbett S, Wurfel MM, Fessler MB. 2014. APOE4 is associated with enhanced in vivo innate immune responses in humans. J Allergy Clin Immunol; doi:10.1016/j.jaci.2014.01.032 [Online 20 March 2014]

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Prevalence of allergies the same, regardless of where you live

By Jacqueline Powell

In the largest, most comprehensive nationwide study to examine the prevalence of allergies from early childhood to old age, NIEHS scientists report that allergy prevalence is the same across different regions of the United States, except in children 5 years and younger.

"Before this study, if you would have asked 10 allergy specialists if allergy prevalence varied depending on where people live, all 10 of them would have said yes, because allergen exposures tend to be more common in certain regions of the U.S.," said Darryl Zeldin, M.D., NIEHS scientific director. "This study suggests that people prone to developing allergies are going to develop an allergy to whatever is in their environment. It's what people become allergic to that differs."

The study appeared online Feb. 9 in the Journal of Allergy and Clinical Immunology and is the result of analyses performed on blood serum data, compiled from approximately 10,000 Americans, in the National Health and Nutrition Examination Survey (NHANES) 2005-2006.

Salo said survey participants also completed a questionnaire with allergy-related questions and allowed researchers to collect dust samples from their homes. (Photo courtesy of Steve McCaw)

No regional difference overall

Although the study found that the overall prevalence of allergies did not differ between regions, researchers discovered that one group of participants did exhibit a regional response to allergens. Among children ages 1-5, those from the southern U.S. displayed a higher prevalence of allergies than their peers living in other U.S. regions. These southern states included Texas, Oklahoma, Louisiana, Arkansas, Tennessee, Kentucky, Mississippi, Alabama, Georgia, West Virginia, Virginia, North Carolina, South Carolina, and Florida.

Zeldin said that NHANES is one of the major survey programs of the National Center for Health Statistics. (Photo courtesy of Steve McCaw)

"The higher allergy prevalence among the youngest children in southern states seemed to be attributable to dust mites and cockroaches," explained Paivi Salo, Ph.D., an epidemiologist in Zeldin's research group and lead author on the paper. "As children get older, both indoor and outdoor allergies become more common, and the difference in the overall prevalence of allergies fades away."

NHANES 2005-2006 not only tested a greater number of allergens across a wider age range than prior NHANES studies, but also provided quantitative information on the extent of allergic sensitization. The survey analyzed serum for nine different antibodies in children ages 1-5, and 19 different antibodies in subjects 6 years and older. Previous NHANES studies used skin prick tests to test for allergies.

Allergic risk factors

The scientists determined risk factors that made a person more likely to be allergic. The study found that in the 6 years and older group, males, non-Hispanic blacks, and those who avoided pets had an increased chance of having allergen-specific IgE antibodies, the common hallmark of allergies.

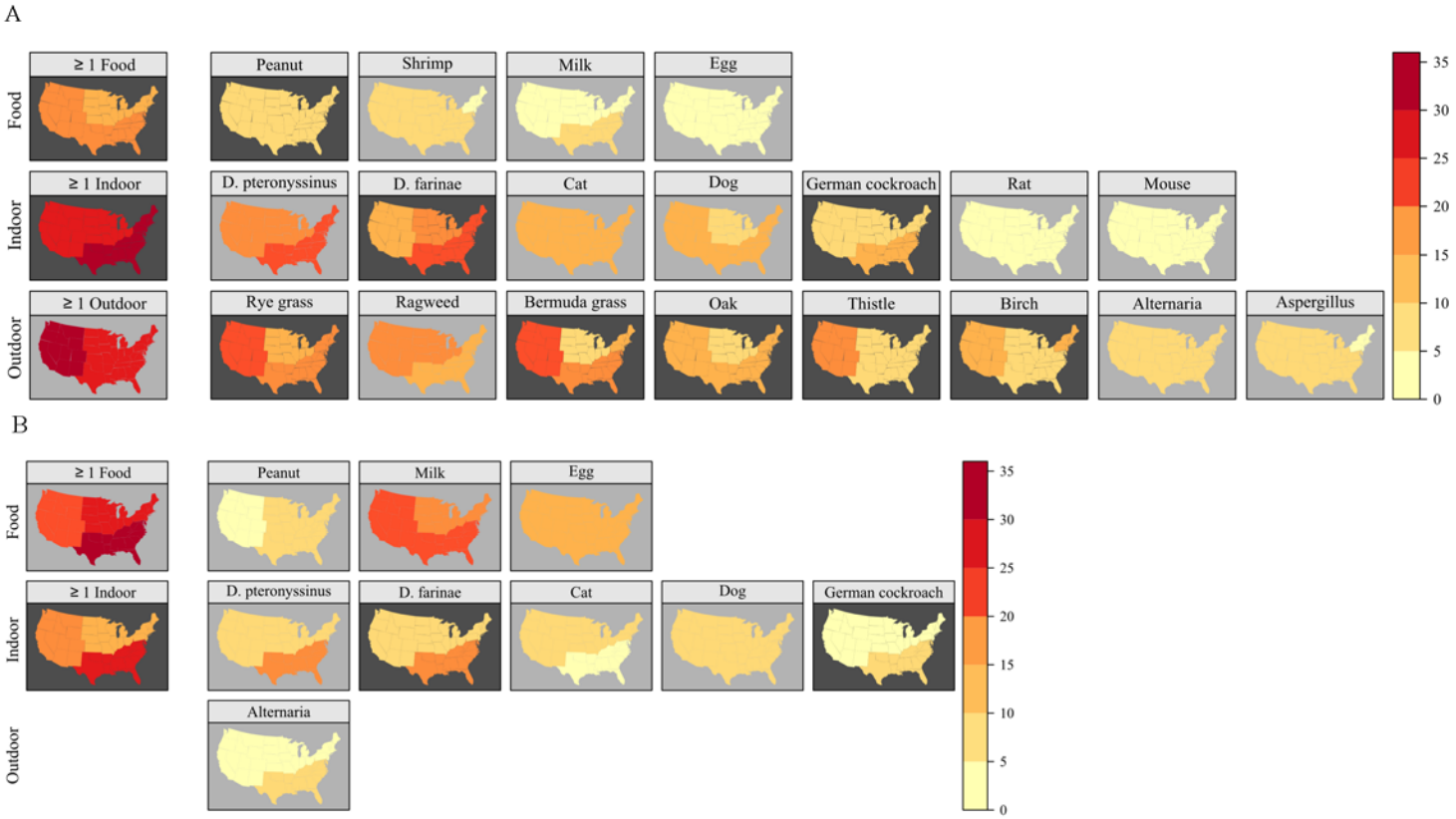
Socioeconomic status (SES) did not predict allergies, but people in higher SES groups were more commonly allergic to dogs and cats, whereas those in lower SES groups were more commonly allergic to shrimp and cockroaches.

By generating a more complete picture of U.S. allergen sensitivity, the team uncovered regional differences in the prevalence of specific types of allergies (see image on next page). Sensitization to indoor allergens was more prevalent in the South, while sensitivity to outdoor allergens was more common in the West. Food allergies among those 6 years and older were also highest in the South.

The researchers anticipate using more NHANES 2005-2006 data to examine questions allergists have been asking for decades. For example, using dust samples obtained from subjects' homes, the group plans to examine the link between allergen exposure and disease outcomes in a large representative sample of the U.S. population.

Citation: Salo PM, Arbes SJ Jr, Jaramillo R, Calatroni A, Weir CH, Sever ML, Hoppin JA, Rose KM, Liu AH, Gergen PJ, Mitchell HE, Zeldin DC. 2014. Prevalence of allergic sensitization in the United States: Results from the National Health and Nutrition Examination Survey (NHANES) 2005-2006. J Allergy Clin Immunol; doi:10.1016/j.jaci.2013.12.1071 [Online 9 February 2014].

(Former NIEHS postdoctoral fellow Jacqueline Powell, Ph.D., is a writer and analyst with Education and Training Systems International.)



Although the overall prevalence of allergies did not differ by region, the study found regional differences for specific allergens and allergen types. The image depicts prevalence of allergen-specific IgE antibodies in participants aged 6 years and older (A), and 5 years and younger (B). (Illustration courtesy of Paivi Salo)

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Obesity primes the colon for cancer

By Sheila Yong

Obesity, rather than diet, causes changes in the colon that may lead to colorectal cancer, according to an NIEHS study published online April 1 in the journal Cell Metabolism. The finding bolsters the recommendation that calorie control and frequent exercise, key to a healthy lifestyle, are also a strategy to lower the risk for colon cancer, the second leading cause of cancer-related death in the United States.

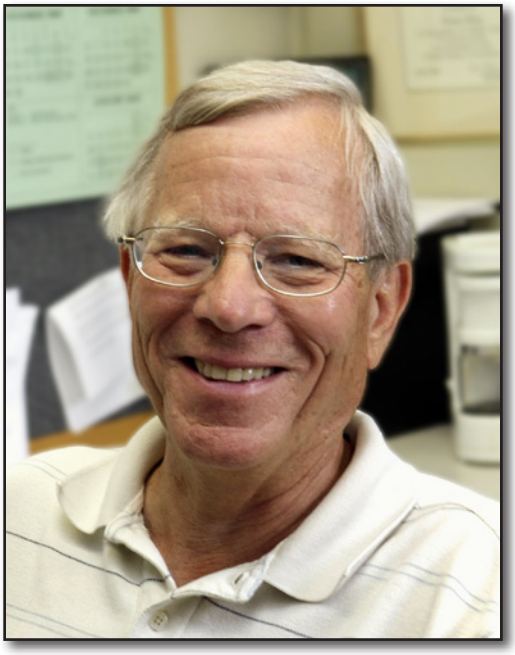
Paul Wade, Ph.D., head of the NIEHS Eukaryotic Transcriptional Regulation Group, and Scientist Emeritus Thomas Eling, Ph.D., head of the NIEHS Eicosanoid Biochemistry Group, led a collaborative team that made the discovery.

According to Wade, the results of the mouse study suggest that being excessively overweight activates signals in the colon that lead to the progression of cancer. (Photo courtesy of Steve McCaw)

NAG-1 gene protects against colon cancer

A large body of scientific literature says people who are obese are predisposed to a number of cancers, particularly colorectal cancer, Eling said. To better understand the processes behind this link,

he and his colleagues fed two groups of mice a diet in which 60 percent of the calories came from lard. The first group of mice contained a human version of a gene called NAG-1, which has been shown to protect against colon cancer in other rodent studies. The second group lacked the NAG-1 gene.



Eling and his group discovered the NAG-1 gene several years ago when they treated mice with nonsteroidal anti-inflammatory drugs. (Photo courtesy of Steve McCaw)

The NAG-1 mice did not gain weight on the high-fat diet, while mice that lacked the NAG-1 gene grew plump. Another striking difference between the two groups of animals was also discovered.

"The obese mice exhibited molecular signals in their gut that led to the progression of cancer, but the NAG-1 mice didn't have those same indicators," Eling said.

The researchers looked for molecular clues by isolating cells from the colons of the mice and analyzing a group of proteins called histones. Histones package and organize DNA in a cell's nucleus, and sometimes undergo a process known as acetylation, in which chemical tags bind to the protein surface. The pattern of acetylation varies depending on the chemical processes taking place in the cell.

Wade explained that the acetylation patterns for the obese mice and the thin NAG-1 mice were drastically different. Patterns from the obese mice resembled those from mice with colorectal cancer. The additional weight they carried also seemed to activate genes associated with colorectal cancer progression, suggesting the obese mice were predisposed to colon cancer.

"Any preexisting colon lesions in these animals are more likely to evolve rapidly into malignant tumors," Wade said. "The same thing may happen in humans."

Determining signaling pathways

Wade and Eling want to find out exactly how obesity prompts the body to develop colorectal cancer. Wade said that the likely candidates for triggering tumor growth are fat cells, but there are many more possibilities. Finding these cellular switches may give lead to improvements in treatment and prevention of colorectal cancer.

"Once we identify the signaling pathways and understand how the signal is communicated, we may be able to design ways to treat colorectal cancer in obese patients," Wade said.

Citation: Li R, Grimm SA, Chrysovergis K, Kosak J, Wang X, Du Y, Burkholder A, Janardhan K, Mav D, Shah R, Eling TE, Wade, PA. 2014. Obesity, rather than diet, drives epigenomic alterations in colonic epithelium resembling cancer progression. Cell Metab:19(4):702-711.

(Sheila Yong, Ph.D., is a visiting fellow in the NIEHS Inositol Signaling Group.)

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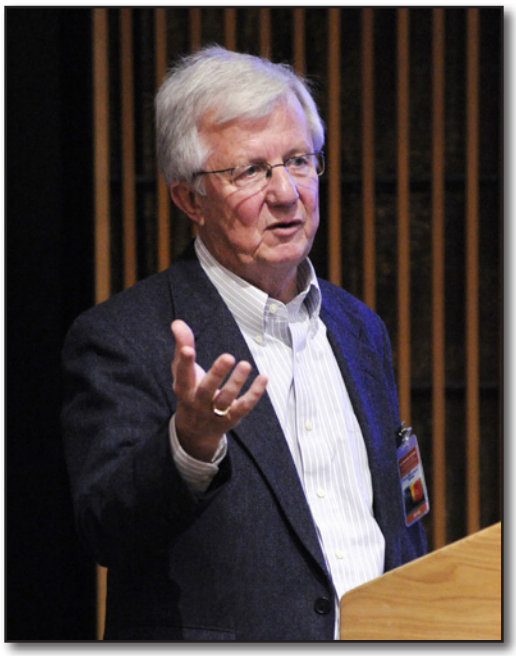
Solving a mystery

By Audrey Pinto

During a seminar March 5, NIEHS-funded environmental toxicologist Richard Peterson, Ph.D., presented pioneering work that implicated dioxin-like chemicals in the mysterious disappearance of lake trout in Lake Ontario in the 1950s. His findings also shed new light on birth defects of the human heart.

For decades, the fishing communities around Lake Ontario knew something was very wrong in the lake. In the 1940s, the lake trout population rapidly declined, and by the 1950s, it was wiped out. Even a restocking campaign in the 1960s and 1970s failed. Yet no one knew just what caused the lake trout to disappear.

Peterson's account of his NIEHS-funded search for the answers was co-sponsored by the NIEHS Office of the Director and Laboratory of Signal Transduction.



Peterson suspected that developing organisms were more susceptible to environmental influences, leading to his insights about the impacts of dioxin on zebrafish embryo hearts. (Photo courtesy Steve McCaw)

It's all in the dioxin

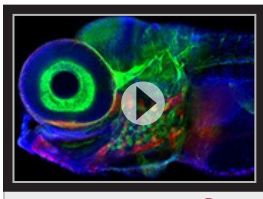
Peterson, deputy director of the NIEHS Center for Developmental and Molecular Toxicology at the University of Wisconsin–Madison (UW), and his research team collaborated with scientists from the U.S. Environmental Protection Agency, searching for answers. They hypothesized that the depletion of lake trout was the result of embryo mortality from exposure to environmental contaminants, specifically 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and related compounds.

"What became clear in the 1970s was that some other event, besides predation of eggs, low genetic diversity, competition, and low stocking densities, was preventing lake trout embryos from developing into viable yearlings that were recruited into the population," said Peterson.

"We had an idea that the recruitment failure was the result of dioxin exposure, and that lake trout embryos were very sensitive to this contaminant," he explained. "But, at the time, we had no toxicological data to support our hypothesis, and we had no idea what the target organ was that caused the near extinction of the lake trout."

Why use zebrafish?

- Mammalian and avian embryos with severe heart defects die rapidly, due to the lack of a functional cardiovascular system.
- Zebrafish embryos are not dependent on a functional cardiovascular system, so zebrafish with severe heart defects survive embryonic development. This allows scientists to study heart malformations.



Linked video:

Watch as Peterson's colleagues, Jessica Plavicki, Ph.D. and Warren Heideman, Ph.D., discuss recent findings on the effects of dioxin on the developing heart. (3:02)

(Launches in new window)

Download Media Player: Flash

Zebrafish with broken hearts

Using dioxin-exposed lake trout embryos, Peterson and his team discovered that TCDD, at environmentally relevant levels of exposure, caused embryo mortality as a result of blue sac disease.

"Blue sac disease in fish embryos is characterized by extensive edema, malformations, and cardiovascular dysfunction, and there is no recovery from this condition," explained Peterson. "It impairs development of the fish embryo heart, resulting in heart failure and mortality." Peterson and his longtime UW collaborator Warren Heideman, Ph.D., demonstrated this in zebrafish.

Taking their team's discovery one step further, they investigated the epicardium, the outer cell layer of the heart. Research had previously suggested that the epicardium contributes to development of the heart valves, outflow tract, and ventricle.

"We postulated that TCDD exposure impairs the development of the zebrafish embryo epicardium, leading to heart malformation and failure," Peterson said. "After one hour of TCDD exposure, the embryo hearts develop normally for the first 48 hours. During this time, no heart toxicity is detected. However, between 48 and 120 hours, right at the time the epicardium is forming, zebrafish embryos show signs of high dioxin sensitivity, which results in heart malformation and heart failure."

Connecting environmental and human health

Concluding his presentation, Peterson noted that some evidence links maternal exposure to hazardous chemicals, like dioxins, with birth defects in humans. For example, one known risk factor for a severe birth defect, hypoplastic left heart failure, is exposure to hazardous chemicals.

"We see striking similarities in the disease process of hypoplastic left heart failure between dioxin-exposed zebrafish embryos and newborns with this disorder," said Peterson. "The human condition also occurs during embryonic development, and results in an abnormally small left ventricle, and impaired heart valves and outflow tract, culminating in heart failure and newborn mortality."

Peterson noted that dioxin exposure assessments are limited in humans, and more research is needed to establish a clear association between dioxin-like chemicals and congenital heart defects in humans.

(Audrey Pinto, Ph.D., is technical editor for the journal Environmental Health Perspectives.)

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New study links BPA and prostate cancer in humans

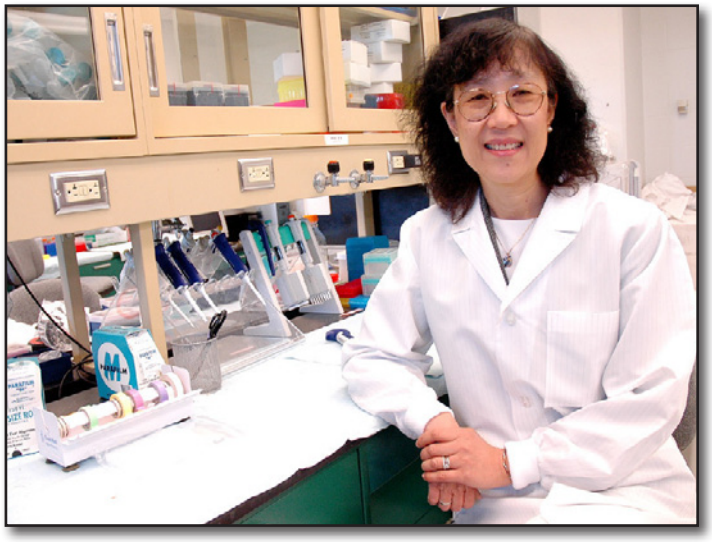
By Staton Wade

A new study by Shuk-mei Ho, Ph.D., and colleagues at the University of Cincinnati (UC), funded in part by NIEHS, provides preliminary evidence of an association between bisphenol A (BPA) exposure and the occurrence of prostate cancer in humans. Until now, the endocrine-disrupting compound BPA was linked to cancer risk in animals, but human, or clinical, data was lacking.

The study, published in the March issue of the journal PLOS ONE, found a significant difference between the levels of BPA in the urine of 27 men with prostate cancer and 33 men without prostate cancer. According to a UC press release, this research provides the first evidence that urinary BPA levels may be a marker for prostate cancer.

Clinical evidence of a BPA-prostate cancer link

Higher BPA levels were associated with low levels of the prostate cancer marker PSA in patients under 65, which has implications for cancer diagnosis. "High levels of BPA exposure may mask early diagnosis, by lowering PSA, creating a false negative," said Ho, director of the Cincinnati Cancer Center, and Jacob G. Schmidlapp, professor and Chair of Environmental Health at the UC College of Medicine.



"Prostate cancer is the second most common cancer among men in North America, and one in six men will develop it over their lifetime," said Ho. "Major contributing factors other than age are race and family history, whereas little is known about the impact of endocrine disruptors on prostate cancer." (Photo courtesy of the University of Cincinnati Medical Center)

Interestingly, the difference between urinary BPA levels was more significant in men under the age of 65. "Higher urinary BPA may be associated with early onset prostate cancer, or may occur because the younger patients belong to a generation born right after BPA was introduced for commercial use," explained Ho.

She also pointed out that BPA exposure is widespread. "High urinary levels indicate lifestyle habits that are conducive to chronic high exposure," she said. "If BPA has effects on prostate cancer development and progression, then removal of the toxicant will be an effective method to ameliorate prostate cancer risk and incidence."

According to Ho, to see a link in this relatively small number of urological patients was surprising. "This supports the need for a larger-scale study — one with long-term clinical follow-up — to confirm the association between BPA and prostate cancer," she said.

In vitro studies suggest potential mechanisms

In addition to the clinical evidence, Ho's research group performed in vitro studies in cancerous and noncancerous prostate cells, to identify potential mechanisms of BPA-induced transformation. Using immunofluorescence, they found an increased rate of abnormalities in the centrosomes, organelles required for cell division, of prostate cells treated with BPA.

Importantly, centrosome abnormalities, a hallmark of malignant transformation, were observed at low levels of BPA exposure. The researchers also observed an increase in the cancer-like growth pattern of one prostate cancer cell line exposed to low doses of BPA.

These findings suggest a mechanism underlying the role of BPA in cellular transformation and disease progression, according to Ho. Further studies are needed to determine if BPA indeed contributes to prostate cancer development, and to better understand the effects of BPA on prostate cells.

Citation: Tarapore P, Ying J, Ouyang B, Burke B, Bracken B, and Ho SM. 2014. Exposure to bisphenol A correlates with early-onset prostate cancer and promotes centrosome amplification and anchorage-independent growth in vitro. PLoS One 9(3):e90332.

(Staton Wade, Ph.D., is an Intramural Research Training Award fellow in the NIEHS Chromatin and Gene Expression Group.)

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Symposium explores cognitive effects of neurotoxic exposures during development

By Monica Frazier

The Duke University Integrated Toxicology and Environmental Health Program (ITEHP) held its spring symposium March 7 on the Duke campus in Durham, N.C. Funded in part by NIEHS, the event was organized and moderated by Duke University Medical Center professors Edward Levin, Ph.D., of the department of psychiatry and behavioral sciences, and Susan Murphy, Ph.D., of the department of obstetrics and gynecology.

Experts in developmental toxicology, medicine, and psychology gave talks on their research and clinical work related to the symposium's theme, "Cognitive Impairment Caused by Developmental Neurotoxic Exposure: Mechanisms, Consequences, and Therapeutic Treatment." The event attracted a capacity audience of researchers and clinicians, including many from NIEHS.

The epidemiologic transition — new focus on chronic diseases

The symposium began with keynote talks by NIEHS grantees Philip Landrigan, M.D., of the Icahn School of Medicine at Mount Sinai, and Frederica Perera, Dr.P.H., Ph.D., of Columbia University, on the vulnerable brains of the developing child.

Landrigan caught the audience's attention with updates on the main neurotoxic culprits in the environment, as well as by highlighting how inadequate regulation allows relatively unstudied synthetic chemicals to be used in products. He also explained what he called the epidemiologic transition, which is a change in focus due to the decrease in frequency and severity of infectious diseases. "Life expectancy has doubled in the past century, so what's happened to replace the infectious diseases are the chronic diseases," he said.

Levin provided a warm welcome to the attendees. He opened the symposium by discussing the many reasons for decreasing developmental neurotoxic exposures, including moral, public health, medical, and economic considerations, as well as national security. (Photo courtesy of Steve McCaw)

Landrigan, who is director of the Mount Sinai Children's Environmental Health Center, enlightened the audience about the lack of testing for new synthetic chemicals before they are used in products in the United States. He encouraged the active participation of Congress, regulators, and interest groups to use scientific evidence to effect policy change. (Photo courtesy of Steve McCaw)

Perera described her work with the Columbia Center for Children's Environmental Health New York City cohort studying the effects of exposure to polycyclic aromatic hydrocarbons on child development. (Photo courtesy of Steve McCaw)

Like Landrigan, Perera and her colleagues are finding that many chronic diseases come from preventable exposure to chemicals in the environment. She described her group's molecular epidemiological studies in New York, Poland, and China, pointing to the effects of maternal hardship and products of combustion on children's cognition and behavior. When changes are made to reduce these exposures, she said, "Everyone benefits."

The far-reaching impacts of toxicity

Exposure to lead was the topic of a presentation by NIEHS grantee Kim Dietrich, Ph.D., of the University of Cincinnati (UC), who was part of the Cincinnati Lead Study. Major research studies have brought attention to the economic and societal costs of lead exposure, which were especially high in urban areas while it was a component of gasoline.

Dietrich explained that children are most exposed to lead during their early years, when hand-to-mouth activity is at its highest. Since lead toxicity has come to the attention of the public, particularly with the link of higher blood levels to IQ deficits, Dietrich and others have also been able to associate blood lead with behavioral issues, including a striking increase in likelihood of criminal behavior.

Duke psychologist Scott Kollins, Ph.D., then talked about the attention deficit-hyperactivity disorder (ADHD) phenotype, pointing to the mass of chemicals whose effects are largely unknown, but appear linked to the dramatic increase in ADHD diagnoses.

Talks continued after lunch with a focus on pesticides, nicotine, and manganese exposures. Levin opened the afternoon session with his talk on the cognitive effects of developmental exposure to pesticides and nicotine in rat and zebrafish models.

Theodore Slotkin, Ph.D., also of Duke, described his findings that prenatal nicotine exposure predisposes the brain to nicotine addiction in adolescence. "Smoking during pregnancy is the cause of transgenerational addiction," Slotkin argued.

NIEHS Deputy Director Rick Woychik, Ph.D., was among Institute scientists attending the symposium. He and others enjoyed discussing the topics during session breaks. (Photo courtesy of Steve McCaw)

NIEHS postdoctoral fellow Maile Henson, Ph.D., was among many NIEHS researchers in attendance. Henson is a member of the Synaptic and Developmental Plasticity Group headed by Serena Dudek, Ph.D. (Photo courtesy of Steve McCaw)

Slotkin gave an afternoon lecture filled with impressive research linking maternal cigarette smoking during pregnancy to her offspring's nicotine addiction in adolescence. (Photo courtesy of Steve McCaw)

Concluding the day of talks was a presentation by UC researcher Charles Vorhees, Ph.D., on cognitive and behavioral effects of developmental exposure to manganese and stress in rats. Vorhees compares the responses of normal and treated rats in swimming tests, using the Cincinnati Water Maze (see story).

Despite progress in understanding the detrimental effects of chemical exposures, symposium speakers agreed that scientists, clinicians, policymakers, and the general public continue to have much work to do, to fully understand the extent of the cognitive effects from past and present exposures, and, most importantly, prevent risky toxicants from being introduced into the environment in the future.

The symposium was co-sponsored by the Duke University ITEHP, Superfund Research Center, and NICHES Children's Environmental Health and Disease Prevention Research Center.

(Monica Frazier, Ph.D., is an Intramural Research Training Award fellow in the NIEHS Mechanisms of Mutation Group.)

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Lecture highlights flame retardants

By Sara Mishamandani

Human exposure to flame retardants in household products and their potential endocrine-disrupting effects were the topics of a talk by Heather Stapleton, Ph.D., March 19 at NIEHS, sponsored by Gregory Travlos, Ph.D., and the NTP Cellular and Molecular Pathology branch. Stapleton and colleagues at the NIEHS-funded Duke University Superfund Research Program (SRP) have conducted a variety of studies on exposure to flame-retardant mixtures, including polybrominated diphenyl ethers (PBDEs) and other chemicals, which are released from furniture and other household items.

An NIEHS Outstanding New Environmental Scientist (ONES) awardee, Stapleton is an associate professor of environmental sciences and policy at the Duke University Nicholas School of the Environment. She also leads a project as part of the Duke SRP. (Photo courtesy of Steve McCaw)

"We have found high levels of PBDEs in household furniture and house dust, and we are very interested in understanding how flame-retardant applications in furniture relate to human exposure and internal dose," said Stapleton. "We are investigating how humans are chronically exposed in the home environment, to better understand the potential health impacts on the population."

Known and alternative flame-retardant chemicals

According to Stapleton, the use of one flame-retardant mixture, known as PentaBDE (PBDE), was phased out in 2004, due to concerns about its tendency to concentrate in human tissues and lead to potential human health effects. Other chemicals are currently used to meet flammability requirements, but little information is available on how people are exposed to these new flame retardants or their potential health effects.

Stapleton and colleagues collected dust samples, blood samples, and hand wipes from a group of children in North Carolina to study exposure to PBDEs. Their findings suggest that toddlers have significant exposure, due to transfer of house dust particles from their hands, and objects such as toys, to their mouths. They also found that there was a strong correlation between the PBDE levels found on the hand wipes and the levels measured in the blood (see story).

Stapleton's lab also tested furniture foam for a long list of chemicals, because many flame-retardant mixtures are proprietary. They found that it contained, on average, about five percent flame-retardant chemicals, by weight. In furniture produced after 2004, the chemical tris (1,3-dichloro-2-propyl) phosphate (TDCPP) was prevalent, likely as a replacement for PBDE. In the 1970s, TDCPP was voluntarily phased out of children's pajamas after studies suggested it had mutagenic properties.

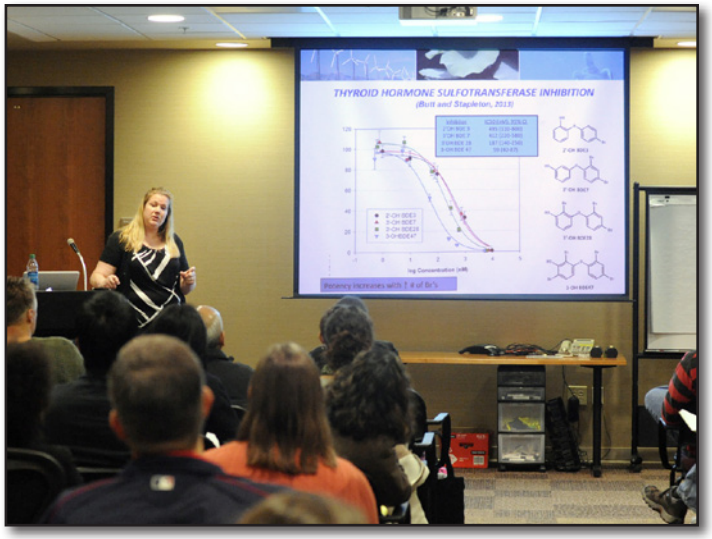
Stapleton worked with another Duke SRP scientist, Theodore Slotkin, Ph.D., to determine if TDCPP might be neurotoxic as well. The study found that TDCPP, as well as other replacement flame retardants may affect neurodevelopment with similar, or even greater, potency than chemicals already known or suspected to be neurotoxicants.

Tackling another flame retardant alternative

The flame-retardant mixture Firemaster® 550 (FM 550) came into use as a replacement for the phased-out PBDE. Stapleton and her research team performed a small-scale study to examine health effects of high and low exposures to FM 550 on pregnant rats.

The study showed that perinatal exposure to FM 550 is associated with endocrine-disrupting effects. The research team observed weight gain, early puberty onset, and cardiovascular health effects at exposure levels lower than the no observable adverse effect level reported by the manufacturer.

"There is a lot of misinformation out there about flammability standards and chemicals used in household products," said Stapleton. "Some furniture manufacturers don't even know what is in their foam, because the mixtures are proprietary. We are continuing to measure foam samples from household products to track human exposure and inform about health risk."



Addressing a capacity audience, Stapleton described the chemicals found in her analysis of furniture foam. Stapleton and her team are working to identify new chemicals used to meet flammability standards, and to understand the health effects of different flame retardant chemical mixtures. (Photo courtesy of Steve McCaw)

Discover the chemicals in your sofa

Scientists at Duke SRP, led by Stapleton, are inviting the general public to be part of this research and learn more about what chemicals may be in their home, by testing furniture samples for flame-retardant chemicals at no cost to the public. Because manufacturers are not required to label products with the flame retardants used, only laboratory testing can determine whether flame retardants are in consumers' home furnishings.

Data collected from this testing will help the research team understand which flame-retardant chemicals are currently used in furniture. They can then study how people are exposed to these chemicals, to better understand if the chemicals may impact human health.

Anyone interested in sending a sample of foam for testing should complete the Submit a Sample form. For more information on the study, visit the Duke Superfund Analytical Chemistry Core website.

(Sara Mishamandani is a research and communication specialist for MDB Inc., a contractor for the NIEHS Superfund Research Program and Division of Extramural Research and Training.)

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Silicone wristbands facilitate exposome study

By Sara Mishamandani

As the environmental health science field strives to better understand the complexity of personal chemical exposures, NIEHS-funded researchers at the Oregon State University (OSU) Superfund Research Program (SRP) led by Kim Anderson, Ph.D., have developed a simple wristband and extraction method that can test exposure to 1,200 chemicals.

The familiar rubbery wristbands that have promoted various causes in recent decades are now being used to archive a person's chemical exposure during a given period of time. (Photo courtesy of Kim Anderson)

While a person wears the silicone wristband, it absorbs chemicals from the air, water, and even the skin. The chemicals remain in the silicone, mimicking the body's absorption process.

Anderson and her colleagues have developed a way to extract and analyze an unprecedented number of chemical compounds from the silicone wristbands after they are worn. They described their methods in a study published March 18 in the journal Environmental Science and Technology.

"Because of its ease of use and the huge number of chemicals that it can sequester, the wristband has opened up the field of passive sampling," said Anderson. Several studies, including one funded by NIEHS in Ohio (see story), are taking advantage of the wristbands to measure individual exposures to environmental chemicals.

Anderson leads a project at the OSU SRP center that focuses on developing new technologies to understand exposure to PAHs and assess the risk they pose for human health. She is also the director of the Food Safety and Environmental Stewardship Program at OSU. (Photo courtesy of Kim Anderson)

Contributing to understanding of the exposome

The combined effects of contaminants from air, water, and food, as well as chemicals produced by the body, complicate efforts to find links between chemical exposures and biological endpoints. Because of this complexity, environmental health researchers worldwide are investigating the exposome, or the measure of a person's lifelong exposure to agents.

"To understand linkages between the exposome and resulting toxicity, researchers are developing new technologies and methods to characterize exposure to an ever larger range of compounds," said Anderson. "With this new device, we can address some questions we haven't been able to address in the past concerning an individual's exposure to a wide range of chemicals."

Testing the samplers in the population

Researchers at OSU provided volunteers with wristbands, to investigate the sensitivity of the samplers and to test compliance issues in both general and occupational populations. Thirty volunteers wore the wristbands, during their day-to-day activities, for 30 days.

Also, eight volunteers, who work as roofers and experience a potentially high occupational exposure to polycyclic aromatic hydrocarbons (PAHs) in roofing tar, wore the wristbands for eight-hour time periods.

After wearing the wristband for 30 days, each volunteer placed the band in a Teflon bag and shipped it to Anderson's lab for analysis.

The researchers detected 49 compounds in the wristbands, including flame retardants, PAHs, phthalates, and pesticides, as well as caffeine, nicotine, and various chemicals found in personal care products.

All of the roofers' wristbands absorbed PAHs, including 12 on a federal priority list of harmful pollutants. Roofers who wore less protection and worked in more enclosed spaces had higher levels of the chemicals on their wristbands.

Steven O'Connell, OSU SRP trainee and lead author on the paper, demonstrates how the wristbands are worn, and why caffeine may be detected in their analysis. (Photo courtesy of Kim Anderson)

"With all volunteers, we found that the samplers had very good analytical sensitivity, and that people will wear the wristband. They are easy to use," said Anderson. "Given just hours of wearing the wristbands, we were able to sequester chemicals with great accuracy."

Anderson and her team are working with a variety of researchers to deploy the wristbands in studies around the country, including a population in an industrial corridor, a community with extensive hydraulic fracturing activity, and a cohort of mothers in their last trimester of pregnancy. The wristbands are also being deployed in separate studies in Peru and West Africa to better understand exposures from agricultural practices and industrial activities.

Citation: O'Connell SG, Kincl LD, Anderson KA. 2014. Silicone wristbands as personal passive samplers. Environ Sci Technol 48(6):3327-3335.

(Sara Mishamandani is a research and communication specialist for MDB Inc., a contractor for the NIEHS Superfund Research Program and Division of Extramural Research and Training.)

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Osteoporosis drug may treat breast and liver cancers

By Tiffany Woods

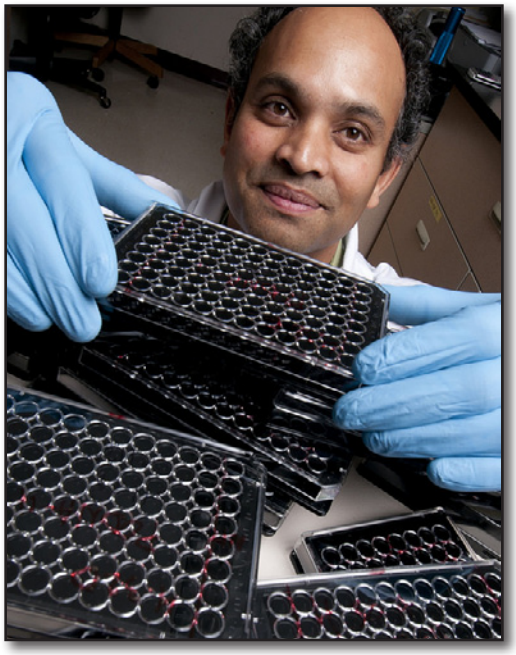
A drug used to prevent and treat osteoporosis in postmenopausal women may also be an effective treatment for some breast and liver cancers, according to a study from Oregon State University (OSU), funded in part by NIEHS, and published Jan. 30 in the journal Cell Death and Disease.

O'Donnell, a postdoctoral scholar at OSU, conducted research that led to the discovery that raloxifene may be an effective treatment for some breast and liver cancers. (Photo courtesy of Tiffany Woods)

Although clinical trials on patients are still needed, researchers found that the drug raloxifene killed human triple-negative breast cancer cells, as well as liver cancer cells. The cells are named triple-negative because they lack receptors for estrogen, progesterone, and a protein known as human epidermal growth factor receptor 2.

Targeting treatment-resistant breast cancers

Triple-negative breast cancers represent about 15-20 percent of all breast cancers in the U.S., and are more common in younger and African-American women, and women who have BRCA1 mutations, according to a factsheet from the Susan G. Komen organization. Chemotherapy, radiation, and surgery are the preferred treatments, because triple-negative breast cancers don't respond to typical medications, such as tamoxifen or trastuzumab.



Kolluri is an associate professor of cancer research at OSU. (Photo courtesy of Lynn Ketchum)

Receptors, which are proteins in or on cells, are like a lock. Hormones act like keys in these receptors to unlock different cellular functions. For example, the hormone estrogen causes uncontrolled proliferation of breast cancer cells by binding to a receptor. Raloxifene blocks estrogen from binding to its receptor and thus keeps breast cancer cells from multiplying.

OSU researchers discovered that raloxifene also binds with a protein called the aryl hydrocarbon receptor (AhR) and kills cancer cells that do not have receptors for estrogen, said Ed O'Donnell, Ph.D., a postdoctoral scholar at OSU who conducted the research.

O'Donnell also analyzed survival data on women who had breast cancers that didn't require hormones to fuel the proliferation of the tumor cells. He found an increased survival rate in the women whose breast cancers had higher levels of the AhR protein.

Repurposing a drug with a nearly 20-year track record

"Our findings are exciting for two reasons," said OSU cancer researcher Siva Kolluri, Ph.D., who led the research team. "No. 1, our research revealed that we can target a specific protein, the AhR, to potentially develop new drugs for liver cancer and a subset of stubborn breast cancers. That's a major goal of our lab. No. 2, we discovered that raloxifene, a known drug, could potentially be repurposed to treat two distinct types of cancers."

The U.S. Food and Drug Administration approved raloxifene for use in bone loss prevention in postmenopausal women in 1997. In 1999, it was approved for treating postmenopausal women with osteoporosis. In 2007, the agency approved the use of raloxifene for reducing the risk of invasive breast cancer in postmenopausal women with osteoporosis, and in postmenopausal women at high risk for invasive breast cancer, which spreads outside the lobules, or milk ducts, into surrounding breast tissue.

Citation: O'Donnell EF, Koch DC, Bisson WH, Jang HS, Kolluri SK. 2014. The aryl hydrocarbon receptor mediates raloxifene-induced apoptosis in estrogen receptor-negative hepatoma and breast cancer cells. Cell Death Dis. 5:e1038.

(This story was adapted from an article by Tiffany Woods, news leader for the OSU Extension and Experiment Station Communications department.)

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Community resilience and disaster response in the U.S. Gulf Coast

By Annah Wyss

"Residents, Responders, and Resilience" was the topic of a Feb. 25 webinar hosted by the NIEHS Partnerships for Environmental Public Health (PEPH) program. The event highlighted NIEHS-funded research on community responses to technological and natural disasters, specifically the Deepwater Horizon oil spill and Hurricane Katrina.

By describing their community-engaged research and workforce development projects in the Gulf Coast region, presenters illustrated how well-built social networks and community engagement enhance the resilience of communities affected by disasters and can help address future health threats.

Mayer uses community-based participatory research to engage local stakeholders in the research process. (Photo courtesy Brian Mayer)

Social capital influences community resilience

Brian Mayer, Ph.D., associate professor of sociology at the University of Arizona, presented on his research funded through the Deepwater Horizon Research Consortia. He opened the webinar by explaining the ways both individual and community level characteristics, including human, economic, social, and political capital, can influence the resilience of populations before and after a disaster.

In their research, Mayer and colleagues compared two counties in Florida impacted by the Deepwater Horizon oil spill. They found that the county with stronger social capital — measured as a network of social ties between various agencies, businesses, and other organizations within and outside the community — experienced a stronger recovery, including more rapid growth in the tourism and seafood industries.

"Community resilience means the capacity of communities to respond positively to crises," said Mayer. "It is the ability of a community to adapt to pressures and transform itself in a way which makes it more sustainable in the future."

Irani also serves as development director of the UF Center for Public Issues Education in Agricultural and Natural Resources. (Photo courtesy University of Florida)

Community-engaged research identifies challenges and solutions

Healthy Gulf Healthy Communities (HGHC), another project funded through the Consortia, identified and engaged community partners who represent the needs of the diverse communities impacted by the Deepwater Horizon disaster. According to Tracy Irani, Ph.D., professor of agricultural communication at the University of Florida (UF), and Sam Mathews, Ph.D., professor emeritus at the University of West Florida, the project illustrates the utility of building networks between individuals and communities.

In April 2012, HGHC sponsored a community forum that brought together members of government, nongovernment, faith-based, and other organizations in the region stretching from the southern coast of Alabama to the western coast of Florida. In 2013, they also conducted community environmental scans. Irani and Mathews analyzed the transcripts from the forum, as well as data from the environmental scans, and identified challenges stemming from the disaster. These included elevated levels of assistance requests, health disparities within communities, and lack of clear planning and communications. Addressing these challenges will better prepare these communities for future disasters.

"Programs need to link from the inside out, not the outside in," Mathews said about efforts to address these community needs before and after a disaster. He stressed the importance of establishing regional community resilience centers to support communication among organizations.

Although retired, Mathews remains involved in research projects such as HGHC. (Photo courtesy Sam Mathews)

Education empowers communities

In addition to technological and man-made disasters, natural disasters have affected communities in the Gulf region in recent years. Ebony Turner, Ph.D., assistant director for education and training at Dillard University's Deep South Center for Environmental Justice (DSCEJ), described several projects her group led to build community resilience in response to Hurricanes Katrina, Rita, and Sandy, as well as the Deepwater Horizon cleanup.

In Houston and New Orleans, the DSCEJ sponsored a workforce development project to train over 100 individuals as construction and remediation workers. The center also supported efforts to replace contaminated soil with sod for 35 homes, as well as several schoolyards and playgrounds in New Orleans. Residents and contractors participated in training on mold remediation, and community members received training in soil remediation and use of personal protective equipment, which proved valuable after Hurricane Katrina and, later, during the Gulf oil spill cleanup.

Turner and the DSCEJ address community and worker resilience in response to natural and man-made disasters, through workforce development and community education and training programs. (Photo courtesy Ebony Turner)

Like the other presenters, Turner and colleagues engaged the communities they serve, to guide response efforts. "You need to hear it from the community. What do they need?" Turner concluded.

(Annah Wyss, Ph.D., is an Intramural Research Training Award (IRTA) postdoctoral fellow with the NIEHS Genetics, Environment, and Respiratory Disease Group.)

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Webinar advances review of TCE

By Ernie Hood

The National Toxicology Program (NTP) sought input from the public March 17, as it prepared to write a draft monograph on its review of trichloroethylene (TCE). Cheryl Siegel Scott, of the U.S. Environmental Protection Agency, moderated the four-hour webinar, which attracted more than 75 participants.

Lunn provides scientific expertise for the overall evaluation of substances for their potential to cause cancer in humans. (Photo courtesy Steve McCaw)

TCE was first listed as reasonably anticipated to be a human carcinogen in the 9th Report on Carcinogens (RoC), issued in 2000. A listing in the RoC does not, by itself, mean that a substance will cause cancer. Many factors, including the amount and duration of exposure, as well as an individual's susceptibility to a substance, play a role in whether a person will develop cancer or not.

New studies lead to reconsideration

TCE is a halogenated alkene used primarily as a metal degreaser, with both occupational and environmental exposures. "Since the last review in 2000, there have been several additional human cancer studies published, so we are going to rereview TCE for possible change in its RoC listing status," said Ruth Lunn, Dr.P.H., director of the Office of the Report on Carcinogens.

The specific purpose of the webinar was two-fold — to gain external scientific input on issues related to the assessment of information on exposure and cancer outcomes in epidemiologic studies of TCE, and to obtain public input on the protocol for preparing the draft RoC monograph on TCE.

Exposure assessment quality

Patricia Stewart, Ph.D., a consultant with Stewart Exposure Assessments LLC, in Arlington, Va., reported the results of her systematic evaluation of the quality of exposure assessments in TCE epidemiologic studies.

Stewart rated the cohort and case-control studies according to several criteria, including occupational measures, exposure assessment methods used, and types of exposure estimates and metrics employed. She also evaluated the studies in terms of likelihood and intensity of exposure.

Guha recently published a study on tetrachloroethylene exposure and bladder cancer risk in the NIEHS journal Environmental Health Perspectives. (Photo courtesy Neela Guha)

Cancer outcome classification

Bernard Goldstein, M.D., from the University of Pittsburgh, spoke about methods used to classify cancer outcomes, specifically lymphohematopoietic cancers.

He cautioned that, particularly in the case of non-Hodgkin lymphoma (NHL), although recent advances and changes in classification of neoplasm subtypes enhance treatment choices, they complicate establishment of direct cause-and-effect relationships between specific chemicals and one of the subtypes of NHL.

According to Goldstein, the classification of subtypes should not preclude grouping of subtypes in certain circumstances. "Is it appropriate to combine cancer incidence of different lymphoid tumors in an epidemiological study or meta-analysis?" he asked. "I happen to think it is."

TCE epidemiological studies

National Cancer Institute (NCI) researcher Mark Purdue, Ph.D., reported on the use of exposure and outcome assessments in TCE epidemiologic studies. He described the various methods used in exposure assessment studies and provided his opinions about which were the best, largely based on how quantitative the measurements were. "When evaluating evidence from cohort and case-control studies of TCE, it's essential to consider the quality of exposure assessment," he noted.

According to Purdue, imperfect exposure sensitivity and specificity can introduce misclassification, which would generally bias toward the null, especially when measuring rare exposures such as TCE.

Stewart, shown here at a 2011 meeting of the GuLF STUDY Scientific Advisory Board, is a contractor to NCI and NIEHS. (Photo courtesy of Steve McCaw)

Public input

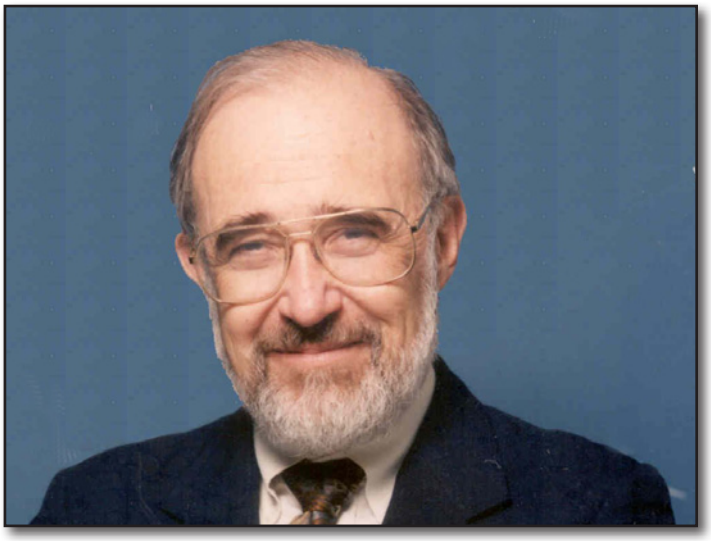
Following the three presentations, the speakers, NTP staff, and members of the public engaged in a discussion, providing further input on the scientific issues that were raised. Neela Guha, Ph.D., of the International Agency for Research on Cancer (IARC) led the discussion, posing a series of questions to the speakers in

four specific areas — exposure metrics and surrogates, and coexposures; exposure levels and response; exposure misclassification and its effects on epidemiological observations; and disease classification of hematological cancers.

Next steps

Lunn noted that the webinar's proceedings would help her group write the cancer evaluation component of the draft monograph. "When that is finished," she said, "we will post it on our website for public comment, and then we plan to hold a peer review meeting for the draft monograph."

(Ernie Hood is a contract writer with the NIEHS Office of Communications and Public Liaison.)



Goldstein, professor emeritus and former dean of the University of Pittsburgh Graduate School of Public Health, is an environmental toxicologist whose research has focused largely on the concept of biological markers in the field of risk assessment. He is board-certified in both hematology and toxicology. (Photo courtesy of the University of Pittsburgh Medical Center)

Purdue is a researcher in the NCI Division of Cancer Epidemiology and Genetics Occupational and Environmental Epidemiology Branch. The potential relationship between TCE and human cancers is one of his lines of research. (Photo courtesy NCI)

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NIEHS scientists contribute to advance in urinary bladder cancer research

By Robin Arnette

NIEHS scientists used their expertise to help identify potential therapeutic targets in more than 100 samples of urinary bladder cancer, as part of the Cancer Genome Atlas Research Network, a large international consortium dedicated to studying the causes of, and finding treatments for, cancer.

Dmitry Gordenin, Ph.D., senior associate scientist in the Laboratory of Molecular Genetics, led the NIEHS contingent, which included David Fargo, Ph.D., head of the Integrative Bioinformatics Group; Steven Roberts, Ph.D., Intramural Research Training Award (IRTA) fellow in the Chromosome Stability Group, and Les Klimczak, Ph.D., a contract researcher at NIEHS. They published their results in the March issue of Nature.

Using sophisticated tools developed at the Institute, they determined that 51 percent of the total mutations in urinary bladder cancers were caused by a class of proteins called apolipoprotein B mRNA-editing enzyme, catalytic polypeptide-like (APOBEC) cytidine deaminases. These proteins normally function in antiviral defense, but can accidentally attack human chromosomes and cause mutations.

One member of this protein family, APOBEC3B, was expressed at high levels in nearly all of the tumor studies, making it the primary suspect for causing mutations. Knowing this, researchers may one day be able to design therapies that prevent the protein from mutating bladder cell DNA.

"We will continue our parallel research of using yeast mutation models and analysis of large cancer datasets to study the complex mix of mechanisms that cause cancer mutations," Gordenin said. "We believe the end results may help develop cancer prevention and therapy strategies."

Citation: The Cancer Genome Atlas Research Network. 2014. Comprehensive molecular characterization of urothelial bladder carcinoma. Nature 507(7492):315-322.

Analysis techniques created at NIEHS

The analytical steps used to determine the frequency of ABOBEC-induced mutations in urinary bladder cancers were employed in earlier research on the causes of cancer.

The method was developed through a collaboration between Gordenin and Roberts, in their hunt for mutations in yeast caused by environmental damage, and Fargo and Klimczak, who took the research one step further by applying bioinformatics approaches.

The method was featured in a 2012 paper published in Molecular Cell and a 2013 article in Nature Genetics.

Gordenin directs several research projects in the NIEHS Chromosome Stability Group, headed by Michael Resnick, Ph.D. (Photo courtesy of Steve McCaw)

Roberts is also a member of the Chromosome Stability Group. (Photo courtesy of Steve McCaw)

Fargo's group promotes and develops bioinformatics tools and resources that empower NIEHS research. (Photo courtesy of Steve McCaw)

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Jetten explores the role of Glis proteins in development and disease

By Kristin Lichti-Kaiser

Anton Jetten, Ph.D., head of the NIEHS Laboratory of Respiratory Biology discussed his research on Gli-similar (Glis) proteins, with the potential of these proteins as novel therapeutic targets in a regenerative approach to treating disease. Jetten spoke March 4 at North Carolina State University.

In his talk, "GLIS Transcription Factors: Mechanism of Action and Roles in Development and Disease," Jetten, discussed his lab's work on the identification and characterization of Glis proteins, their physiological function, and their role in the development of diabetes and kidney disease.

Jetten began by reviewing the discovery of Glis proteins by his group. He explained how this three-member family of Kruppel-like transcription factors regulates gene transcription. Kruppel-like transcription factors are a set of DNA-binding proteins that regulate gene expression.

GLIS proteins, gene-environment interaction, and human disease

Mutations in the genes GLIS1, GLIS2, and GLIS3, which govern the production of Glis proteins, are associated with a broad spectrum of human diseases. Mutations in GLIS1 have been associated with coronary artery disease and Parkinson's disease, and mutations in GLIS2 have been associated with nephronophthisis, a genetic disorder of the kidney. Mutations that inactivate GLIS3 contribute to a multisystem disorder characterized by diabetes, hypothyroidism, and cystic kidney disease.

Certain DNA sequence variations, called single nucleotide polymorphisms (SNPs), in GLIS3 are associated with increased risk for diabetes. Jetten found that several of these are present at a high frequency in a group of North Carolina patients. "Genetic factors, like SNPs in GLIS3, together with environmental factors, such as obesity, high-fat diet, or environmental exposures to chemicals, may promote the development of glucose intolerance and the risk for diabetes," he said.

Jetten is also a member of the affiliated faculty at the NIH Center for Regenerative Medicine, which supports research into the applications of stem cell biology to address the causes, rather than the symptoms, of diseases. (Photo courtesy of Steve McCaw)

Physiological functions of Glis proteins

To study the physiological function of Glis proteins, Jetten and his group developed several mouse models, where the genes for the proteins were inactivated, or knocked out. While the GLIS1 knockout mice displayed no overt phenotype, or obvious clinical features, GLIS2 and GLIS3 knockout mice provided excellent models for studying the role of the proteins in diabetes and kidney disease.

GLIS3 knockout mice died prematurely, due primarily to the development of neonatal diabetes and showed a dramatic loss of insulin-producing beta cells, which are critical for maintaining normal blood glucose levels.

"To understand the role of GLIS3 in different diseases, we have to know what the target genes are in different tissues," said Jetten. He then provided evidence that GLIS3 directly regulates neurogenin 3 and insulin gene expression, factors that are critical in the development of beta cells and the maintenance of their function.

Therapeutic potential in regenerative medicine

A current experimental approach for the treatment of diabetes involves stem cell replacement therapy. Given the physiological role of GLIS3 in beta cell development, Jetten is interested in how the role of GLIS3 in the differentiation of stem cells into insulin-producing beta cells could be used therapeutically. As researchers learn more about the function of GLIS3, Jetten hopes that this protein will become a valid therapeutic target for the treatment of diabetes. "It's likely that upstream signals regulate GLIS3 activity, and one of our major goals at the moment is to understand what those upstream signals are," he said.

In contrast to current state-of-the art insulin replacement therapies, Jetten looks forward to the development of a way to address the long-term complications of diabetes. "If we know what these signals are, we may have a tool to increase GLIS3 activity and enhance insulin production, and this could be a strategy to be used in the future for therapy."

(Kristin Lichti-Kaiser, Ph.D., is an Intramural Research Training Award (IRTA) fellow in the NIEHS Cell Biology Group.)

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This month in EHP

The April issue of Environmental Health Perspectives (EHP) highlights concerns with unlabeled lead content in decorative paints, even after its ban for residential use, as well as the environmental and health impacts of the Navajo Nation's shift to owning, rather than leasing, surface coal mine operations on its land.

http://twitter.com/ehponline

Lead in decorative paints

Decades ago, developed nations began banning lead-based paint for residential use. Yet, few developing countries regulate lead in paint. Decorative paints with high lead content remain readily available on store shelves in these countries, rarely bearing any labeling to warn consumers of the dangers they pose. An international effort is currently underway to remove lead from decorative paints once and for all.

Navajo Nation and coal mining

In January 2014, the Navajo Nation shifted from leasing all its coal-rich land to outside mining companies, to ownership, by purchasing one of its remaining surface coal mines. The controversial purchase was a bid to stabilize the tribe's economy, but critics believe the health and environmental costs of continued coal use will outweigh the economic benefits.

Featured research and related news articles this month include:

- **Associations of Filaggrin Gene Loss-of-Function Variants With Urinary Phthalate Metabolites and Testicular Function in Young Danish Men** — Chinks in the Armor? Filaggrin-Depleted Skin Could Increase Environmental Exposures

- **Birth Outcomes and Maternal Residential Proximity to Natural Gas Development in Rural Colorado** — Birth Defects and Mothers' Proximity to Natural Gas Development: Is There a Connection?

- **Outdoor Air Pollution, Preterm Birth, and Low Birth Weight: Analysis of the World Health Organization Global Survey on Maternal and Perinatal Health** — Apples to Apples: Comparing PM 2.5 Exposures and Birth Outcomes in Understudied Countries

- **An Integrated Risk Function for Estimating the Global Burden of Disease Attributable to Ambient Fine Particulate Matter Exposure** — Disease Burdens Associated with PM 2.5 Exposure: How a New Model Provided Global Estimates

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Extramural papers of the month

By Nancy Lamontagne

- Preterm birth might increase risk for type 2 diabetes
- DDT metabolite linked to higher Alzheimer's risk
- Phthalate exposure trends from 2001 to 2010
- Grasp protein aids protective function of p53 in skin

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

Preterm birth might increase risk for type 2 diabetes

Researchers, supported in part by NIEHS, found that premature infants are more likely to have elevated insulin levels at birth and into early childhood than are infants born at term. Since elevated insulin levels can be an indication of insulin resistance, the findings suggest that preterm birth could be a risk factor for future development of insulin resistance and type 2 diabetes.

The researchers measured plasma insulin levels of 1,358 children at birth and in early childhood. They found that plasma insulin levels were higher in children born before full term. Average insulin levels at birth were 9.2 micro international units per milliliter for full term (39 weeks or later) and 18.9 micro international units per milliliter for early preterm (less than 34 weeks) births. In early childhoos, plasma insulin levels were higher for children born early term (37-38 weeks), late preterm (34-36 weeks), and early preterm than for those born at full term.

The fact that the higher levels of plasma insulin at birth could be tracked into early childhood strengthens the argument for a trajectory of diabetes risk that begins very early in life, according to an accompanying editorial. It also points to the need for rigorous studies of early life interventions, to better understand how to reduce risk for noncommunicable diseases, such as diabetes.

Citation: Wang G, Divall S, Radovick S, Paige D, Ning Y, Chen Z, Ji Y, Hong X, Walker SO, Caruso D, Pearson C, Wang MC, Zuckerman B, Cheng TL, Wang X. 2014. Preterm birth and random plasma insulin levels at birth and in early childhood. JAMA 311(6):587-596. (Editorial)

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DDT metabolite linked to higher Alzheimer's risk

In one of the first studies to identify a strong environmental risk factor for Alzheimer's disease, NIEHS grantees report that patients with Alzheimer's have significantly higher levels of a dichlorodiphenyltrichloroethane (DDT) metabolite than people without the disease. Researchers also found evidence of a gene-environment interaction, as well as a possible mechanism for the pesticide's effects.

In the United States, DDT was used extensively as an insecticide from the 1940s through 1972, and it persists in the environment today. DDT continues to be used in other countries to control malaria. DDE, a DDT metabolite, accumulates in the body as people grow older.

The study compared 86 Alzheimer's patients from Georgia and Texas with 79 healthy elderly people, and found that DDE levels were 3.8-fold higher in the blood serum of the patients with Alzheimer's. DDE levels in the highest range were associated with an odds ratio of 4.18 for increased risk of Alzheimer's, as well as lower scores for the Mini-Mental State Examination (MMSE), a test used to screen for cognitive impairment.

The researchers also looked at the role of the apolipoprotein E (APOE) genotype. They found that among those with the highest DDE levels, participants who carried the APOE4 allele, or form of the APOE gene, had MMSE scores 1.753 points lower than those who carried the APOE3 allele, indicating that carriers of an APOE4 allele may be more susceptible to the effects of DDE.

The researchers also exposed cultured neuronal cells to DDT and DDE, at levels observed in highly exposed people in the United States, and observed an increase in amyloid precursor protein, which is linked with Alzheimer's, indicating a possible mechanism for the association between DDT exposure and Alzheimer's.

Citation: Richardson JR, Roy A, Shalat SL, von Stein RT, Hossain MM, Buckley B, Gearing M, Levey AI, German DC. 2014. Elevated serum pesticide levels and risk for Alzheimer disease. 2014. JAMA Neurol 71(3):284-290. Story

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Phthalate exposure trends from 2001 to 2010

An NIEHS grantee and colleagues report that Americans are being exposed to significantly lower levels of some phthalates and higher levels of others. Phthalates, used to make plastic more flexible, are found in hundreds of consumer products. A federal law that took effect in 2009 permanently banned some phthalates, banned others from use in children's articles such as toys, and set an interim ban, pending further study, on three phthalates, barring their use in toys that can be placed in a child's mouth.

To examine how phthalate exposure is changing over time, the researchers combined data on 11 phthalate metabolites from 11,071 participants in five cycles of the Center for Disease Control National Health and Nutrition Examination Survey. From 2001 to 2010, the researchers found decreases in exposures to permanently banned phthalates — butylbenzyl phthalate, di-n-butyl phthalate, and di(2-ethylhexyl) phthalate (DEHP). Children showed consistently higher DEHP exposures than adults, but the difference between the age groups lessened over time.

Exposures increased for the phthalates under the interim ban — di-n-octyl phthalate by 15 percent, diisodecyl phthalate by 25 percent, and diisononyl phthalate (DiNP) by nearly 150 percent. The increase in DiNP is likely because industry is using it to replace banned phthalates. Exposure tripled for diisobutyl phthalate (DiBP), which hasn't been subject to federal restrictions. DiBP may be replacing diethyl phthalate (DEP), which was a focus of early activism regarding chemicals in cosmetics. Exposure to DEP decreased 42 percent.

The researchers say that the trends they observed are difficult to explain, but may reflect the effects of legislative activity, as well as advocacy efforts of nongovernmental organizations on consumer behavior and the use of phthalates in consumer products.

Citation: Zota AR, Calafat AM, Woodruff TJ. 2014. Temporal trends in phthalate exposures: findings from the National Health and Nutrition Examination Survey, 2001-2010. Environ Health Perspect 122(3):235-241. Story

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Grasp protein aids protective function of p53 in skin

Research, funded in part by NIEHS, revealed that the Grp1-associated scaffold protein, or Grasp, helps the P53 tumor suppressor gene to function correctly in skin. Finding ways to maintain or increase the effectiveness of Grasp could offer an important new avenue for human cancer therapies.

The researchers created mice that lacked the Grasp gene and compared how these mice and normal mice reacted to the mild environmental stress of ultraviolet light, similar to moderate sun exposure. The mice lacking Grasp began to develop cellular abnormalities much more rapidly than ordinary mice. Significantly, mutated skin cells did not die as they should have. In normal mice, the same moderate light exposure caused a rapid increase in expression of the Grasp gene, allowing the p53 protein to stay in the nucleus, and normal protective mechanisms to do their work. Overall, these results suggest that a physiological role of Grasp may be to regulate skin homeostasis after UVB exposure, potentially by influencing p53-mediated apoptotic responses in skin.

Citation: Venkataraman A, Coleman DJ, Nevrivy DJ, Long T, Kioussi C, Indra AK, Leid M. 2014. Grp1-associated scaffold protein regulates skin homeostasis after ultraviolet irradiation. Photochem Photobiol Sci 13(3):531-540.

(Nancy Lamontagne is a science writer with MDB Inc., a contractor for the NIEHS Division of Extramural Research and Training.)

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Intramural papers of the month

By Kimberly Cannady, Deacqunita Diggs, Simone Otto, and Bailey Schug

- Allergy prevalence the same in U.S., no matter where you live
- DNA polymerase mu has a novel mechanism for binding DNA
- MBD3 studies suggest NuRD complex regulates chromatin structure
- MicroRNA expression levels differ in breast cancer patients

Allergy prevalence the same in U.S., no matter where you live

Scientists from NIEHS have shown the prevalence of allergies is the same, regardless of where you live in the U.S., except in children 5 years and younger. The researchers analyzed blood serum data from approximately 10,000 Americans in the National Health and Nutrition Examination Survey (NHANES) 2005-2006. The findings constitute the largest and most comprehensive nationwide study to examine allergy prevalence from early childhood to old age.

The survey analyzed serum for nine different antibodies in children aged 1-5, and 19 different antibodies in participants 6 years and older. While the overall prevalence of allergies did not differ between regions, except in early childhood, allergies to specific allergens and allergen types varied regionally. Allergies also tended to aggregate in clusters of allergens that were similar.

Males, non-Hispanic blacks, and those who avoided pets had an increased chance of having allergies, among those 6 years and older. Children aged 1-5 from the southern U.S. displayed a higher prevalence to allergies than their peers living elsewhere. Although socioeconomic status (SES) did not predict allergies, allergies to dogs and cats were more common in higher SES groups, whereas allergies to cockroaches and shrimp were more common in lower SES groups. **(BS)**

Citation: Salo PM, Arbes SJ Jr, Jaramillo R, Calatroni A, Weir CH, Sever ML, Hoppin JA, Rose KM, Liu AH, Gergen PJ, Mitchell HE, Zeldin DC. 2014. Prevalence of allergic sensitization in the United States: Results from the National Health and Nutrition Examination Survey (NHANES) 2005-2006. J Allergy Clin Immunol; doi:10.1016/j.jaci.2013.12.1071 [Online 9 February 2014]. [Story]

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DNA polymerase mu has a novel mechanism for binding DNA

NIEHS researchers have discovered a novel mechanism by which a DNA polymerase can bind and repair DNA. Polymerase mu is a template-dependent polymerase, like Pol beta and Pol lambda. Previous work investigating Pol beta and Pol lambda emphasized conformational changes and kinetic checkpoints considered crucial for correct DNA repair. Pol mu preserves sequence during a type of double-stranded DNA repair, known as V(D) J recombination, used to make the immunoglobulin light chains necessary for B cells. It is also important in development and DNA repair.

To determine the structure of Pol mu, scientists created a truncated polymerase and characterized its structure during its catalytic cycle. They found minimal conformational change, other than repositioning of loop 1. The rigidity of the overall polymerase, combined with the flexibility of loop 1, allows Pol mu to bind and stabilize the DNA ends of double strand breaks with discontinuous structure. Thus, Pol mu can interact with a selection of DNA substrates with varying structures. To verify that loop 1 is important in substrate selection, scientists mutated specific residues. The resultant loss of activity on specific types of substrates supports the importance of loop 1. **(SO)**

Citation: Moon AF, Pryor JM, Ramsden DA, Kunkel TA, Bebenek K, Pedersen LC. 2014. Sustained active site rigidity during synthesis by human DNA polymerase mu. Nat Struct Mol Biol 21(3):253-260.

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MBD3 studies suggest NuRD complex regulates chromatin structure

NIEHS scientists and their collaborators determined that Mi-2/nucleosome remodeling and histone deacetylase (NuRD) complex regulates chromatin structure, by changing the location or chemical properties of the nucleosome, a building block of chromatin. The researchers performed localization studies to map methyl-CpG binding domain protein 3 (MBD3), a component of NuRD complex, within the genome. This work highlights the importance of understanding NuRD function, since mutations within the complex frequently occur in cancer.

The researchers used DNA adenine methyltransferase identification (DamID) and chromatin immunoprecipitation, coupled with massive parallel sequencing (ChIP-seq), to map MBD3 localization in two breast cancer cell lines. Accessing histone modification data from the ENCODE project, the authors defined the genomic chromatin features bound by MBD3. They observed cell-type specific MBD3 localization patterns at the promoters, gene bodies, and enhancers of active genes. Moreover, they discovered that depletion of MBD3 results in the decrease of nucleosome occupancy at promoter and enhancer regions.

Overall, these studies suggest a role for MBD3, and thus the NuRD complex, in regulating chromatin structure. The researchers propose that this data provides a good starting point to begin addressing the mechanisms through which NuRD modulates the epigenetic landscape. **(KC)**

Citation: Shimbo T, Du Y, Grimm SA Dhasarathy A, Mav D, Shah RR, Shi H, Wade PA. 2014. MBD3 localizes at promoters, gene bodies and enhances of active genes. PLoS Genet 9(12):e1004028.

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MicroRNA expression levels differ in breast cancer patients

According to NIEHS researchers and their collaborators, the expression patterns of serum microRNAs (miRNAs), small, non-coding, single-stranded RNAs, differed between women who later developed cancer versus those who remained cancer free. The scientists examined blood samples obtained from 410 participants in the Sister Study, a nationwide cohort of more than 50,000 women whose sister had breast cancer. It is the first study to use specimens collected before the onset of disease, known as a prospective collection.

The study examined blood from 205 women who subsequently developed cancer, and 205 who did not. Using Affymetrix arrays, the authors detected 414 miRNAs and determined that 21 of 414 miRNAs were significantly different in women who developed breast cancer. Three miRNAs from this group, miR-18a, miR-181a, and miR-222, had the highest expression in a small, independent replication study. In addition, there was some evidence that circulating miRNAs were correlated with the type and severity of the tumor that subsequently developed in the women.

The authors noted that while it may be possible to use miRNAs as an early detection tool, further studies that utilize a larger sample size, as well as specimens from women without a family history of breast cancer, are needed. **(DD)**

Citation: Godfrey AC, Xu Z, Weinberg CR, Getts RC, Wade PA, DeRoo LA, Sandler DP, Taylor JA. 2013. Serum microRNA expression as an early marker for breast cancer risk in prospectively collected samples from the Sister Study cohort. Breast Cancer Res 15(3):R42.

(Kimberly Cannady, Ph.D., is an Intramural Research Training Award (IRTA) fellow in the NIEHS Chromatin and Gene Expression Group. Deacqunita Diggs, Ph.D., is a research fellow at the U.S. Environmental Protection Agency. Simone Otto, Ph.D., is an IRTA fellow in the NIEHS Ion Channel Physiology Group. Bailey Schug studies health promotion at Appalachian State University and is an intern with the NIEHS Office of Communications and Public Liaison.)

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Inside the Institute

NIEHS to upgrade exterior lighting to LED

By Kelly Lenox

In March, the NIH Office of Research Facilities announced plans to upgrade all NIEHS exterior road and walkway lighting to LED. The move supports the Institute's environmental stewardship and sustainability principles, including environmentally responsible facilities operations, pollution prevention, and conservation of energy, among others.

Current lighting, left, will be replaced by LED fixtures, right, increasing visibility, saving on cost, and reducing environmental impact. (Images courtesy of Kyle Hawkins)

"This project was originally developed to address the aging infrastructure of the existing lighting system, but with the advance of LED technology, it became cost effective to upgrade the lighting at the same time," said Kyle Hawkins, mechanical engineer with the NIH Office of Research Facilities at NIEHS.

Not only will the new lights be brighter and safer, they will reduce CO2 emissions equivalent to taking 53 cars permanently off the road. The project will also reduce waste. ORF estimates there will be 1,474 fewer mercury-containing bulbs discarded over the next 20 years, thus eliminating mercury from entering the environment from campus lights.

The project, anticipated to begin in late March and last about 6 months, will be carried out in phases, to stagger road closings and minimize traffic and parking impacts. Regular schedule updates and a campus map showing affected areas will be provided on a weekly basis during construction.

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National Institute of Environmental Health Sciences

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