National Institute of Environmental Health Sciences

Environmental Factor

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October 2014

NIEHS Spotlight

Birnbaum leads delegation to Dioxin 2014

NIEHS and National Toxicology Program Director Linda Birnbaum, Ph.D., led a delegation of 7 scientists to the international symposium Aug. 31-Sept. 5 in Madrid.

Council meeting — from tributyltin to tribal health disparities

The 143rd meeting of the National Advisory Environmental Health Sciences Council included two science talks and updates on NIEHS research and activities.

International epidemiology conference shares NIEHS research themes

NIEHS staff and grantees were active at the International Society for Environmental Epidemiology meeting, which shared institute research priorities.

ISEE workshop offers insights on NIEHS grant awards

A preconference funding workshop helped ISEE attendees better understand NIH grants, particularly those related to environmental epidemiology.

Healthy People 2020 webinar highlights respiratory research at NIEHS

Lead researcher Steven Kleeberger, Ph.D., was one of two experts featured Sept. 18 in a Healthy People 2020 webinar on respiratory diseases and environmental quality.

Clinical Feature

Coating carbon nanotubes reduces lung injury risk

Researchers at NCSU and the NIEHS Clinical Research Unit found that coating carbon nanotubes with aluminum oxide reduces lung injury.

Science Notebook

NIEHS grantee kicks off high-profile lecture series at NIH Video

NIEHS grantee Andrew Feinberg, M.D., was the featured speaker Sept. 3 at the opening talk in the 2014-2015 NIH Wednesday Afternoon Lecture Series.

Baden shares saga of translation — from toxin to treatment and prevention

NIEHS grantee Daniel Baden, Ph.D., opened the 2014 Integrated Toxicology and Environmental Health Program lecture series Aug. 31 at Duke University.

Data science holds the future of cutting-edge analyses Video

Scientists at an NIEHS mini-symposium shared ways data science supports autism diagnosis, genetics of the microbiome, and undiagnosed diseases.

NIEHS Spotlight

NIEHS marks Breast Cancer Awareness Month

NIEHS joins individuals and organizations across the U.S. in support of Breast Cancer Awareness month in October.

Trainees celebrate NIEHS Postdoc Appreciation Week

A week of activities, including workshops, appreciation, and fun, celebrate the key role trainees play at NIEHS.

Oregon State University Superfund program completes pilot assistance project Video

Curriculum on mercury and environmental health is the first product of a program to assist communities affected by Superfund sites.

Town hall event explores ways to increase research funding

The meeting Sept. 2 was the first public event organized by the newly reinstated North Carolina Triangle Chapter of the Society for Neuroscience.

University of Massachusetts junior faculty visit NIEHS to find a home for their research

Junior faculty from the University of Massachusetts Amherst visited NIEHS Sept. 12 to discover how their research fits in with the mission of the institute.

Compatible mining to protect vulnerable populations and the environment

An NIEHS-supported international conference set up a regional hub to promote mining practices compatible with human health, the environment, and local culture.

Science Notebook

Trainee Barbara Nicol honored by Women Scientist Advisors

For young female FARE winners, receiving an NIH Women Scientist Advisors Committee Scholar Award means being named one of the best of the best.

Advisory committee gives thumbs up to progress on alternative methods

The Scientific Advisory Committee on Alternative Toxicological Methods met Sept. 16, giving strong approval to progress made in the last year.

Adverse outcome pathway workshop generates enthusiasm and collaboration

Participants from industry to special interest groups explored the use of adverse outcome pathways to reduce, refine, or replace animal use in toxicity testing.

TSPO — a biomarker of brain injury and inflammation

Tomas Guilarte, Ph.D., intrigued the NIEHS inflammation faculty with the promise of TSPO as a marker for inflammation in the brain and other organs.

NIEHS scientists consider the future of mammalian reproduction

NIEHS had 12 participants, five of whom gave invited talks, at the inaugural Gordon Research Conference on Mammalian Reproduction Aug. 10-15.

Inside the Institute

NIEHS celebrates years of service with 2014 honorees

Birnbaum recognized dozens of NIEHS and NTP staff Sept. 8 for 10, 20, 30, and 40 years of service, as well as those who retired in the past year.

Future NIH administrative leaders visit NIEHS

Several NIH Management Interns and Presidential Management Fellows spent a day exploring NIEHS and learning about working at the institute.

NIEHS launches 2014 CFC drive

The Combined Federal Campaign launched two months of activities Sept. 17, encouraging employees to give to their favorite charities.

Science Notebook

This Month in EHP

The October issue of Environmental Health Perspectives explores remote-sensing technology and using science to inform risk perception.

Distinguished Lecture Series to feature Thomas Platts-Mills

Video

Renowned allergist Platts-Mills, who linked red meat allergies to bites from certain ticks, among other discoveries, will speak at NIEHS Oct. 14.

Extramural Research

Extramural papers of the month

- DNA methylation maps of early embryo development
- Perinatal lead exposure linked to obesity
- Oxidative stress predicts hip fracture
- AhR controls endotoxin tolerance pathway

Intramural Research

Intramural papers of the month

- NTP involved in study of testosterone production in fetal rat
- Mechanisms of scar formation in lung cells after exposure to nanoparticles
- SIRT1 regulates retinoic acid signaling and stem cell differentiation
- Histone-fold domain protein NF-Y promotes chromatin accessibility for cell specification
- Duking it out? My CA2 made me do it

Calendar of Upcoming Events

- **Oct. 2**, Rodbell Auditorium 9:00-10:00 a.m. — NIEHS Office of the Director seminar featuring Christopher Austin, M.D., director of the National Center for Advancing Translational Sciences, speaking on “Catalyzing Translational Sciences”

- **Oct. 6**, Rodbell Auditorium 10:00-11:00 a.m. — Keystone Science Lecture Seminar Series presentation on “Evaluation of the Economic Impact of the NIEHS Worker Training’s Minority Worker Training Program to Improve Public Health,” by Bryan Engelhardt, Ph.D.

- **Oct. 9**, Rodbell Auditorium 8:00 a.m.-5:00 p.m. — North Carolina Society of Toxicology Fall Meeting, register

- **Oct. 10 (Offsite event)**, Environmental Hall Field Auditorium at Duke University, noon–1:30 p.m. — Integrated Toxicology and Environmental Health Program Fall 2014 Seminar Series featuring Sven-Eric Jordt, Ph.D., discussing “Counter-irritation by Menthol: Pharmacological Targets and Implications for Smoking Initiation”

- **Oct. 14**, Rodbell Auditorium 11:00 a.m.–noon — NIEHS Distinguished Lecture Series featuring Thomas Platts-Mills, M.D., Ph.D., on “Epidemics of Allergic Disease 1870–2010: Hay Fever, Asthma, Peanut Allergy, and Now Delayed Anaphylaxis to Red Meat”

- **Oct. 14**, Executive Conference Room noon–1:00 p.m. — Receptor Mechanisms Discussion Group with David Miller, Ph.D., discussing “Regulation of Blood-Brain Barrier Xenobiotic Transporter Expression by Xenobiotics”

- **Oct. 21 (Offsite event)**, Toxicology Building, Room 2104, Centennial Campus of North Carolina State University, 4:00 p.m.–5:00 p.m. — Environmental and Molecular Toxicology Program Seminar Series, featuring Suzanne Fenton, Ph.D., topic TBA

- **Oct. 24 (Offsite event)**, Searle Center Lecture Hall at Duke University, 8:30 a.m.–4:00 p.m. — Integrated Toxicology and Environmental Health Program Fall Symposium, “Low Dose Effects/Non-Monotonic Responses of Endocrine Disruptors,” register

- **Oct. 27**, Rodbell Auditorium 11:00 a.m.–noon — Reproductive and Developmental Toxicology Laboratory Special Seminar, “Characteristics of Function, Expression, and Modulation by Flavonoids,” by Hiroaki Yuasa, Ph.D.

- View More Events: NIEHS Public Calendar

NIEHS Spotlight

Birnbaum leads delegation to Dioxin 2014

By Eddy Ball

NIEHS and National Toxicology Program (NTP) Director Linda Birnbaum, Ph.D., led a delegation of 7 scientists to Dioxin 2014 Aug. 31-Sept. 5 in Madrid. The event marked the 34th anniversary of this major international symposia series highlighting research into scientific and public health aspects of exposure to halogenated persistent organic pollutants in the environment.

Birnbaum, right, was joined by her husband David, who travelled to Madrid at his own expense, at the Dioxin 2014 banquet Sept. 4. (Photo courtesy of Linda Birnbaum)

"Dioxin 2014 will continue in the tradition of previous symposia as the leading international conference for scientists, regulators, and exhibitors presenting recent advances in all areas of halogenated persistent organic pollutants," wrote symposium chair Begona Jimenez, Ph.D., of the Spanish National Research Council. "We are very fortunate to have received more than 650 short papers, from 41 countries, that will be presented at this meeting."

At the start of her week in Madrid, Birnbaum made a presentation on the toxicology of tetrabromobisphenol A (TBBPA) during the symposium's daylong Flame Retardant Science and Policy side meeting Aug. 31, where Green Science Policy Institute representatives unveiled The Madrid Statement on Poly- and Perfluoroalkyl Substances. That evening, along with five other senior scientific experts, she was a panelist at the popular Science With Tapas forum for students — one of several events reflecting the Dioxin 2014 theme, "Our Students, Our Future."

In the course of the symposium, which formally opened Sept. 1, Birnbaum participated in three themed sessions and two poster sessions, presenting NIEHS and NTP research on chemicals used in fire retardants and plastics, as well as research from her own National Cancer Institute-funded laboratory (see text box). On the final full day of the meeting, she presented a thought-provoking re-examination of dose response in risk assessment, along with a novel integrated approach to hazard identification.

In keeping with its student-centered motto, Dioxin 2014 wrapped up Sept. 5 with the presentation of Otto Hutzinger Student Awards and a look ahead to Dioxin 2015, scheduled for Aug. 23-28 in Sao Paulo.

Next generation risk assessment

As the meeting neared its finale, several discussions highlighted theoretical, policy, and regulatory themes. In the Sept. 4 session on Integrating Toxicology and Epidemiology for Risk Assessment, Birnbaum looked forward to an emerging paradigm of integrated toxicology that recognizes complex dose response, as she examined the implications of "Environmental Exposures, Endocrine-disrupting Chemicals, and New Approaches to the Science of Risk Assessment."

In her presentation, Birnbaum outlined evidence supporting the concept of nonmonotonic dose response of organisms to hormones and hormone-like chemical exposures, where the shape of the dose response curve reverses as the level of contamination goes up. To help support her proposal for an integrated risk assessment, she cited several authorities, including the Endocrine Society, U.S. Environmental Protection Agency, and European Commission.

This pattern in dose response means that low levels of exposure to endocrine-disrupting compounds can have disproportionate effects on human health. In contrast, for chemicals that exhibit the more traditional monotonic dose response, toxicity steadily increases with dose. According to Birnbaum, the traditional risk assessment framework, based on monotonic dose response, needs to be expanded to accommodate newer research findings about the specific mechanisms at work in the endocrine system.

"The question is no longer whether nonmonotonic dose responses are real," she maintained. "Instead, the question is which dose-response shapes should be expected for specific environmental chemicals and under what specific circumstances."

Birnbaum concluded her talk with an additional proposal for advancing hazard identification, with the adoption of systematic review to address the breadth of relevant data from human, animal, and mechanistic studies. She presented a four-step approach to hazard evaluation, based on a model now used by NTP, that quantifies confidence levels for the body of evidence of adverse health effects resulting from environmental exposures.

Showcasing research from NIEHS and NTP

Birnbaum and members of her lab at NIEHS — the Toxicology and Toxicokinetics Group — presented "Biological Effects of Tetrobromobisphenol A (TBBA) in Female Wistar Han Rats," during the Is TBBPA Safe? session Sept. 1, which she also co-chaired. She was joined by NTP toxicologist Michael Sanders, Ph.D.; postdoctoral fellow Gabriel Knudsen, Ph.D.; and laboratory technician Sherry Coulter.

The TBBPA session also included a presentation by a team of NTP scientists, reporting on findings that "Uterine Tumors are Induced in Rats After Exposure to Tetrabromobisphenol A, a Commonly Used Flame Retardant." The team included toxicologist June Dunnick, Sanders, and pathologist Susan Elmore, D.V.M.

During a Sept. 2 session on Industrial, Occupational and Accidental Exposure, Birnbaum joined an international group of colleagues to discuss "Biomonitoring of Selected Halogenated Organics and Metals in Vietnamese Women Electronic Waste Incinerator Workers."

During a poster session on Food and Feed: Evaluation of Dietary Intake later that day, she and her co-authors communicated their findings on "Exposure to Bisphenol A (BPA) From Fresh, Frozen, and Canned Food from Dallas, Texas, U.S.A." Birnbaum's lab group also participated in the Toxicology and Mechanisms: Dioxins and Dioxin-like Chemicals poster session, with a study tracing "Biological Fate of the Emerging Brominated Flame Retardants, 2-Ethylhexyl Tetrabromobenzoate (TBB) and Bis(2-ethylhexyl) Tetrabromophthalate (TBPH) in Female Sprague Dawley Rats."

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Council meeting — from tributyltin to tribal health disparities

By Kelly Lenox

Birnbaum, shown in her Yupik dress, shared evidence of exposures faced by tribal communities throughout the U.S. (Photo courtesy of Steve McCaw)

The 142nd meeting of the National Advisory Environmental Health Sciences Council kept a brisk pace, covering topics ranging from the fiscal year 2015 budget and a new grant mechanism, to addressing tribal health disparities. The Sept. 9-10 meeting also featured science talks on connections between manufacture of artificial butter flavoring and lung disease, and the transgenerational obesogenic effects of tributyltin (see sidebar on right and text box).

Scientific advances and community connections

Opening the meeting, NIEHS and National Toxicology Program (NTP) Director Linda Birnbaum, Ph.D., reviewed legislative activities, and shared key scientific publications, highlighting cross-divisional collaboration. "Our term, one NIEHS, refers to the interactive nature of our science program, with scientists in different divisions working together," Birnbaum told council members.

She also noted the National Academy of Sciences validation of two recent NTP listing decisions in the 12th Report on Carcinogens (see related story). Other news included two new environmental health core centers, at Wayne State University and Texas A&M University. Birnbaum also addressed prospects for the fiscal year 2015 budget, saying that a continuing resolution, with funding through mid-December, appears likely.

NTP scientist discusses applied research

Dan Morgan, Ph.D., lead researcher in the NTP Laboratory Respiratory Toxicology Group, briefed the council on research into the connection between artificial butter flavoring, or diacetyl, and a lung disease known as bronchiolitis obliterans, or popcorn lung, an irreversible fibrotic disease of the small airways in the lung most commonly associated with lung transplant patients.

Diacetyl is present in low concentrations in many foods, from microwave popcorn to cake mixes. It is considered a safe food ingredient, but in the food industries where the products are made, workers may be exposed to much higher concentrations via inhalation. After several workers developed the disease, the United Food and Commercial Workers International Union nominated diacetyl for study by NTP, and Morgan's group began work to characterize the inhalation toxicology, obtain inhalation exposure data, and research disease development, to help in designing treatments.

Researchers determined that inhalation exposure to diacetyl led to development of bronchiolitis obliterans in rats, and to development of a possible precursor condition in mice.

Morgan noted that after their findings were published and provided to regulatory agencies, certain products began appearing on grocery shelves labeled as containing no diacetyl. But they still claim butter flavor, raising the question of safety of the substitute compounds. His group performed inhalation studies and found that 2,3-pentanedione had effects similar to those of dicetyl. "The longer chain substance, 2,3-hexanedione, was considerably less toxic," Morgan said.

Ongoing studies seek to identify the pathway by which airway fibrosis develops when these compounds are inhaled, to help identify possible treatments, and to further understand the source of the difference in response of mice and rats.

Council member Andrew Feinberg, M.D., of Johns Hopkins University, observed how often NIEHS-funded research relates to issues in the geographic area of the grantee institution. "It's very important to make sure that, at the local level, people know that NIEHS is supporting these programs," he said.

"I give Dr. Collins a great deal of credit for getting the word out that biomedical research is an engine of innovation and change, and great for local economies," Birnbaum responded.

Genomic data sharing and innovative grant design

Gwen Collman, Ph.D., director of the NIEHS Division of Extramural Research and Training, focused her presentation on two new NIH developments.

A new genomic data sharing policy will make data collected during NIH-funded research available to other researchers. Detailed information on the new policy is posted on the Genomic Data Sharing website.

A new grant mechanism has been introduced that will provide sustained and flexible support to experienced investigators who have outstanding records of research productivity. Collman explained that the R35 grant mechanism will give researchers more freedom to break new ground or extend previous discoveries in new directions.

Collman closed by reviewing research activities tied to the NIEHS strategic plan, including targeted research programs, workshops, and other activities that promote the exchange of ideas and scientific findings.

Budget process and scientific peer review

Two members of the NIEHS Office of Management, Laurie Johnson, head of the Financial Management Branch, and Scott Redman, deputy budget director, clarified the budget process, from development within the institute through Congressional appropriation.

Alfonso Latoni, Ph.D., chief of the NIEHS Division of Extramural Research and Training Scientific Review Branch, outlined the process for review of grant applications and contract proposals.

Collman, right, shown with Pat Mastin, Ph.D., deputy director of the NIEHS Division of Extramural Research and Training, answered a question about the R35 application process. "The information in the application will be different, supporting the review of career accomplishments of the principal investigator and their relevance to the future research focus," she said. (Photo courtesy of Steve McCaw)

Latoni shared challenges of the scientific review process. "In a time of continually evolving science, we need to align our review panels with the state of the science," he said. (Photo courtesy of Steve McCaw)

Environmental health disparities in tribal communities

Donning a traditional dress of the Yupik residents of St. Lawrence Island, Alaska, where she held community forums this summer (see story), Birnbaum underscored the NIEHS concern over the contribution of the environment to health disparities, consistent with Goal 6 of the NIEHS strategic plan. She provided specific examples of these disparities, gleaned from her trip last year to the Navajo Nation, and research talks given at a grantees' meeting in June at Salish Kootenai College in Montana.

Birnbaum described environmental health threats faced by the Alaska tribal communities she visited and shared the outcome of meetings with regional health care providers. "In Anchorage, health care providers responded positively to our message of threats [tribal communities] face from environmental exposures," said Birnbaum. "And in Nome, [public health officials] agreed to send a team of health care providers to St. Lawrence Island."

Council member Vi Waghiyi shared the community-based research done by the Alaska Community Action on Toxics, helping to address the unique environmental exposures in the far north. "We have a cancer crisis," Waghiyi said, elaborating on efforts to get assistance in resolving health disparities. "It was an honor to have Dr. Birnbaum visit. It's hard to get health care providers to recognize the health impacts we're seeing," she said.

Council member Tomas Guilarte, Ph.D., met with the NIEHS Inflammation Faculty after the meeting concluded, to discuss potential biomarkers for inflammation (see story). (Photo courtesy of Steve McCaw)

"Organotins are potent activators of two nuclear receptors that are key to adipogenesis, and they do it at parts per billion levels," Blumberg said in his talk. (Photo courtesy of Steve McCaw)

Feinberg spoke up after Birnbaum's presentation. "I love hearing about all the science," he said. "What a great way to start." (Photo courtesy of Steve McCaw)

Council members Edward Postlethwait, Ph.D., of the University of Alabama, and Vivian Cheung, M.D., of the Howard Hughes Medical Institute, were active participants in the sessions, asking clarifying questions and injecting a little humor into the proceedings. (Photo courtesy of Steve McCaw)

"For 13 years, Alaska Community Action on Toxics has enabled us to do our own research, so we can improve the health and well-being of our Yupik people," Waghiyi said. (Photo courtesy of Steve McCaw)

Addressing Birnbaum, Elizabeth Yeampierre, J.D., executive director of UPROSE, shared responses to her social media posts from the council meeting. "I want to thank you for your leadership, because it's been noted from New York City to New Orleans to Alaska," she said. "It's not just symbolic — today when you were talking about food deserts, the language you spoke referred directly to the experience we're having." (Photo courtesy of Steve McCaw)

Tributyltin — early life obesogen?

Bruce Blumberg, Ph.D., professor of developmental and cell biology at the University of California, Irvine, spoke to the council about his work on environmental chemicals that may contribute to obesity, or obesogens, particularly tributyltin. Blumberg argued that changes in the balance between exercise and food intake are not adequate to explain the obesity epidemic.

Blumberg's research is concerned with endocrine-disrupting chemicals and how they might contribute to lifelong obesity, and whether effects may be heritable. His early work on nuclear hormone receptors led to an interest in in these chemicals. Two receptors in particular appear to play a role in the development of obesity.

His group has been particularly interested in organotins, especially tributyltin, because it is well accepted as an endocrine disruptor. After determining that tributyltin causes a number of effects that would lead to adipogenesis, or fat cell formation, they turned to looking at the effects of early life exposure.

They found an increased number of fat cells, larger fat cells, and increased expression of relevant genes for up to three generations in mice exposed prenatally to tributyltin.

Blumberg's group is now conducting further analyses, seeking to identify epigenetic effects that may be responsible for this transgenerational effect. "The bottom line message is that the existence of such things as obesogens strongly shifts the paradigm. We have to go for prevention," Blumberg said.

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International epidemiology conference shares NIEHS research themes

By Joe Balintfy

More than a dozen NIEHS staff and numerous grantees were among the 1,100 attendees and presenters at the 26th Annual International Society for Environmental Epidemiology (ISEE) Conference, Aug. 24-28 in Seattle, Washington. Scientific work presented at the conference highlighted the theme of understanding environmental health from local to global perspectives, with a particular emphasis on research that informs policy, according to organizers from the Department of Environmental and Occupational Health Sciences at the University of Washington School of Public Health.

"There was a big emphasis on trying to get students and trainees to the meeting," said conference co-chair, Joel Kaufman, M.D., professor of environmental and occupational health sciences, medicine, and epidemiology at the university, and an NIEHS-funded researcher. He added that the society wanted to include a diverse group of researchers, not only from North America and Europe, where the society has major representation, but also from less developed countries.

Collman said that the online tools described in presentations on the global burden of disease were impressive and showed how epidemiological and population data could be shared. (Photograph courtesy of Steve McCaw)

Aligned with NIEHS goals

There were more than 120 sessions, symposia, and meetings throughout the conference. NIEHS scientists from across the institute gave presentations about their work, including studies of respiratory symptoms in oil spill clean-up workers in the Gulf Long-term Follow-up Study, a symposium about integrating the microbiome, a morning session on using personal monitoring tools to measure exposure, and a presentation about the complexity of environmental exposures and their links to health effects.

"Environmental epidemiology research makes up more than 25 percent of all research supported by NIEHS," said Gwen Collman, Ph.D., director of the NIEHS Division of Extramural Research and Training (DERT). "Research grants from NIEHS also provide a training environment for many graduate students and postdocs," she continued. "ISEE is the one scientific meeting which brings together all of these population scientists and trainees and allows for intense interaction between program and review staff and our grantees."

Kimberly Gray, Ph.D., NIEHS health scientist administrator, spoke of the cookstove presentation by Anindita Dutta, Ph.D., from the Energy and Resources Institute, New Delhi, India. "It dovetailed nicely with the most recent National Toxicology Program cookstove meeting, NIH efforts in cookstoves, and the scientific emphasis area of the World Health Organization-NIEHS Collaborating Centre." (Photo courtesy of Steve McCaw)

Connecting with the epidemiology community

Many NIEHS grantees contributed to ISEE sessions and oral poster presentations. Presentations by NIEHS grantees included Carmen Marsit, Ph.D., of Darmouth College, who discussed the approaches that the Dartmouth Children's Environmental Health and Disease Prevention Research Center uses to look at the effects of arsenic on behavior, through placental DNA methylation.

Christine Loftus, a student in the University of Washington School of Public Health, presented work on ammonia exposures in an agricultural community and pediatric asthma mortality. Her research was funded by one of the original NIEHS Research to Action grants, to Catherine Karr, M.D., Ph.D., an associate professor of Environmental and Occupational Health Sciences and Pediatrics at the university.

Allan Just, Ph.D., of the Harvard School of Public Health, discussed a poster on an approach to reconstructing long- and short-term exposure to air pollution, for epidemiological studies in highly polluted areas.

The next ISEE conference is scheduled for Aug. 30-Sept. 3, 2015, Sao Paulo, Brazil.

(Joe Balintfy is a public affairs specialist in the NIEHS Office of Communications and Public Liaison.)

Kaufman, echoing Collman, said of the global burden of disease plenary, "[It was] very interesting and exciting and highlighted a lot of new visualization tools which are available." (Photo courtesy of University of Washington)

Richard Kwok, Ph.D., right, of the NIEHS Chronic Disease Epidemiology Group, said the meeting was also a great way to network with fellow epidemiologists, share best practices, and get help and ideas for collaboration and problem solving. Sara Mishamandani, left, of MDB, Inc., an NIEHS contractor, and Danielle Carlin, Ph.D., from the Superfund Research Program at NIEHS also attended the meeting. (Photo courtesy of Joe Balintfy)

In his plenary talk, former NIEHS Director Kenneth Olden, Ph.D., pointed out although genetic changes happen over thousands of years, epigenetic changes allow for faster adaptations, and almost every human disease is associated with epigenetic changes. (Photo courtesy of University of Washington)

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ISEE workshop offers insights on NIEHS grant awards

By Caroline Dilworth

A preconference workshop at the International Society for Environmental Epidemiology annual meeting in Seattle (see related story) helped students and new researchers understand how to navigate the National Institutes of Health (NIH) grant funding system. Workshop attendees also received more specific information about environmental epidemiology grant opportunities.

"The workshop was a great opportunity for NIEHS staff to meet emerging researchers and start forming relationships that will hopefully span a career," said Gwen Collman, Ph.D., NIEHS Division of Extramural Research and Training director.

After participating in the grant workshop, Chadwick co-chaired a microbiome symposium at ISEE. (Photo courtesy of Joe Balintfy)

NIH grant funding basics

Lisa Steele, Ph.D., scientific review officer for the NIH Infectious, Reproductive, Asthma, and Pulmonary Conditions Study Section, explained how grants are reviewed at the Center for Scientific Review. She also introduced attendees to the center's Early Reviewer Program, which allows qualified early-stage scientists without prior experience with the center to participate in the peer review process, so that they may become well-trained reviewers and more competitive as applicants. The program also helps enrich the existing pool of NIH reviewers.

Lisa Chadwick, Ph.D., health scientist administrator in the NIEHS Genes, Environment, and Health Branch, provided participants with information on funding mechanisms relevant to early-stage researchers, including fellowships for predoctoral and postdoctoral students, and career development awards. NIEHS Scientific Review Branch Chief Alfonso Latoni, Ph.D., detailed how career awards and other review activities are conducted at NIEHS. Throughout the workshop, presenters stressed the value of having mentors with a proven track record and relevant expertise, as well as a strong research plan.

Dilworth, right, shown with presenter Lu Chen, Ph.D., from New York University, opened the workshop with an overview of the grant process. (Photo courtesy of Joe Balintfy)

Opportunities for environmental epidemiology

Kimberly Gray, Ph.D., health scientist administrator in the NIEHS Population Health Branch shared a broad overview of programs and specific research opportunities relevant to environmental epidemiology, along with Gary Ellison, Ph.D., of the National Cancer Institute. Gray highlighted the NIEHS Research to Action program, which encourages community-academic partnership to address environmental concerns of communities. She also reviewed the NIEHS Outstanding New Environmental Health Scientist Award, supporting research and career enhancement of exceptional early stage researchers in the environmental health field.

Claudia Thompson, Ph.D., chief of the Population Health Branch, closed the workshop, remarking that attendees should feel free to reach out to NIEHS staff in the future. “Interacting with students and new researchers is a really enjoyable part of our job,” she said.

Attendee Shelley Ehrlich, M.D., Sc.D., from Cincinnati Children’s Hospital Medical Center, appreciated the opportunity to attend the event. “I really enjoyed the workshop — it was very helpful,” she said.

(Caroline Dilworth, Ph.D., is a health scientist administrator in the Population Health Branch, where she co-directs the extramural environmental epidemiology program.)

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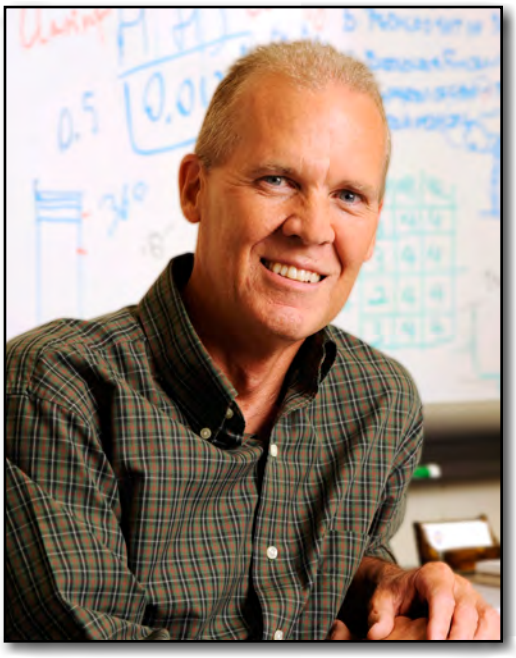
Healthy People 2020 webinar highlights respiratory research at NIEHS

By Eddy Ball

NIEHS lead researcher Steven Kleeberger, Ph.D., was one of two experts featured Sept. 18 in a Healthy People 2020 webinar on respiratory diseases and air quality. The speakers explored the impact of the environment on health and progress in data, communication efforts, and effective implementation strategies.

Kleeberger, who heads the Environmental Genetics Group at NIEHS, discussed research conducted in labs at the institute and by academic researchers elsewhere, through NIEHS grants. He was joined by Virginia Lau, advanced projects advisor for the Bay Area Air Quality Management District in California, who described air quality improvements realized through translation of research findings into regulations and community outreach.

U.S. Department of Health and Human Services Director of the Office of Disease Prevention and Health Promotion Don Wright, M.D., moderated the panel discussion. Experts from the department filled in for Acting Assistant Secretary of Health Wanda Jones, Dr.P.H., who was unable to participate as scheduled, and contributed to the question-and-answer session and roundtable discussion.



Kleeberger also discussed the complexity of the developmental origins of respiratory disease that manifests later in life. “We believe that there are some very critical windows [of susceptibility to exposures], particularly during pregnancy, on the fetus,” he said. (Photo courtesy of Steve McCaw)

Research efforts

NIEHS takes part in the Healthy People 2020 initiative as the co-lead agency on the environmental health topic area and is one of three National Institutes of Health agencies leading the respiratory diseases topic area. The program’s most recent progress update shows marked progress in the two environmental quantified health indexes that relate to air quality.

During his overview of work supported by NIEHS, Kleeberger described research that is unraveling the mystery of why people react differently to exposure to air pollution. As he explained, some people with the same exposures develop complex lung diseases, such as asthma, chronic obstructive pulmonary disease, and acute respiratory distress syndrome, whereas others do not. “One of the risk factors that has been identified is genetic background,” he explained, referring to studies by his group and others.

"We [also] know that genetics cannot account for all of the increase in asthma prevalence," he added. He pointed to ongoing research into the ways other host characteristics, such as age, immune status, nutrition, and complex environmental exposures, influence health conditions.

Implementation at the community level

Lau is part of the regional government agency that regulates sources of air pollution within the nine San Francisco Bay Area counties, one of the state's and the nation's hot spots for air pollution. She told an inspiring story of community action, a campaign to raise awareness, and new regulations on diesel emissions that have led to substantially better air quality. By 2014, they saw an estimated reduction of 86 percent in particulate matter emissions from trucks shipping goods, from 2007 baseline levels.

Together, government and citizens in the Bay Area used research findings, including the type of work Kleeberger described in his presentation of NIEHS research, to inform their air quality improvement efforts. The resulting action plan included anti-idling campaigns, traffic diversion efforts, incentives, and new regulations on the efficiency of diesel engines used in trucks, trains, and ships operating in the Bay Area.

"One agency cannot do all of the work by itself," Lau said of her group's partnership with citizen groups and the California Air Resources Board. "The key to real success is that people are working together."

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NIEHS marks Breast Cancer Awareness Month

By Eddy Ball

NIEHS joins individuals and organizations across the U.S. in support of Breast Cancer Awareness month in October. Visitors to the NIEHS website will notice several special features marking its recognition, in addition to ongoing programs and research to better understand and prevent breast cancer.

Breast Cancer Awareness Month is organized by major breast cancer charities every October to increase awareness of the disease and to raise funds for research into its cause, prevention, diagnosis, treatment, and cure.

NIEHS initiatives

NIEHS supports research on the environmental causes of breast cancer and, with its partner, the National Cancer Institute, devoted $35 million from 2003 to 2010 to the national network of NIEHS Breast Cancer and the Environment Research Centers at major universities and research institutes.

In 2010, the initiative entered its second phase, the Breast Cancer and the Environment Research Program, which will hold its 2014 annual meeting Nov. 19-21 in San Francisco. The program supports a multidisciplinary network of scientists, clinicians, and community partners to examine the effects of environmental exposures that may predispose a woman to breast cancer in later life.

Along with in-house research on breast cancer and cancer-related mechanisms in several labs at NIEHS, the Epidemiology Branch at NIEHS conducts the ongoing Sister Study. The study is prospectively examining environmental and familial risk factors for breast cancer and other diseases in a cohort of 50,000 cancer-free sisters of women diagnosed with breast cancer.

NIEHS maintains an environmental health topics section online, with user-friendly information on breast cancer.

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Trainees celebrate NIEHS Postdoc Appreciation Week

By Jordan St. Charles

NIEHS trainees celebrated National Postdoc Appreciation week Sept. 15-19, with a host of events organized by the Office of Fellows Career Development Director Tammy Collins, Ph.D., and the NIEHS Trainees Assembly. Events, which included workshops, appreciation, and fun, kicked off Monday with "Scientists Teaching Science," a 2-hour workshop run by Barbara Houtz, a consultant for the National Institute of Health (NIH) Office of Intramural Training and Education, and culminated with an afternoon of trivia and ice cream on Friday.

Trainees, from left, Natalie Saini, Ph.D., Thuy-Ai Nguyen, Ph.D., and Maria Shatz, Ph.D., joke together during the trivia challenge. Their team, The p53 Shades of Grey, won the Most Humorous Team Name award. (Photo courtesy of Steve McCaw)

Celebration and support

Events celebrated trainees in different ways. Collins held an orientation for new fellows on Monday, and on Tuesday, the Environmental Factor team held an appreciation event for the trainee writers who contribute to the publication.

On Wednesday, Denise Saunders, Ph.D., a consultant for the NIH Office of Intramural Training and Education, led a workshop entitled "Cultivating Optimism: Maintaining Resilience in the Job Search."

"The seminar was a great discussion on how to identify ways to help you stay positive during what is often the long, exhausting process of searching for the next position after your postdoc," said Monica Frazier, Ph.D. "Denise's suggestions will be very beneficial when I begin the process."

Science writing career opportunities highlighted

On Thursday, Deepa Singh, Ph.D., of the Mechanisms of Mutation Group, hosted the first in the 2014-2015 Brown Bag Lunch series. Jacqueline Powell, Ph.D., and Jillian Orans, Ph.D., met with a group of trainees to discuss "Life in the Science Writing/Editing Industry." Powell is a former NIEHS Intramural Research and Training Award fellow in neurobiology. She is currently working at Education and Training Systems International (ETSI) and will soon be at Impact Pharmaceutical Services. Orans is a former postdoc from Duke University, currently working at Camargo Pharmaceutical Services.

Both Powell and Orans described the medical writing profession as family friendly. They observed that a large part of medical writing also encompasses regulatory writing. Orans said that she was able to gain regulatory experience through an internship at Camargo Pharmaceutical Services. Powell reported believing that the experience that she gained at ETSI was instrumental in getting a position at the more regulatory oriented Impact Pharmaceutical Services.

Birnbaum opened the celebration, emphasizing how important trainees are to research at NIEHS. (Photo courtesy of Steve McCaw)

An afternoon of trivia and ice cream

The celebration on Friday started with the current trainees posing for a group photo. Afterwards, NIEHS and National Toxicology Program Director Linda Birnbaum, Ph.D., opened the trivia session with a few comments about how integral postdocs are to research at NIEHS.

Tammy Collins led the trivia, which included questions on turophilia, or the love of cheese, Speak Like a Pirate Day, and the Ebola virus genome. In the end, the "Matrix Reloaded" team had the most trivial knowledge and won the game.

Prizes were also given for team names, including the Most Scientific Name — Behavioral Phenotypes; the Most Humorous Name — p53 Shades of Grey; and the Most Environmental Name — The Toxic Avengers.

(Jordan St. Charles, Ph.D., is an Intramural Research and Training Award fellow in the DNA Replication Fidelity Group at NIEHS.)

NIEHS Trainees Assembly members Maile Henson, Ph.D., and Katie O'Brien, Ph.D., serve ice cream, generously donated by the NIEHS lead researchers. (Photo courtesy Steve McCaw)

Collins led the trivia event. (Photo courtesy of Steve McCaw)

The "Matrix Reloaded" team, composed of, from left, Stravros Garantziotis, M.D., Jaime Cyphert, Ph.D., Vandy Stober, Collin Johnson, and Carol Trempus, won the trivia event. (Photo courtesy of Steve McCaw)

The Behavioral Phenotypes team, from left, Serena Dudek, Ph.D., Shannon Farris, Ph.D., Kelly Carstens, Danny Lustberg, Maile Henson, Ph.D., and, not shown, Chad Osterlund, Ph.D. and Palmyra Romeo, took home not only their good attitudes, but also both The Most Scientific Name and Last Place awards. (Photo courtesy of Steve McCaw)

The trainees gathered with Birnbaum before playing the trivia game on a beautiful, late summer day. (Photo courtesy Steve McCaw)

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Oregon State University Superfund program completes pilot assistance project

By Sara Mishamandani

A tool to educate K-8 students about mercury in the environment and its effects on human health is now online, thanks to collaboration between the NIEHS Superfund Research Program at Oregon State University, the U.S. Environmental Protection Agency (EPA), and the London School in Cottage Grove, Oregon.

An EPA Partners in Technical Assistance Program pilot project for the Black Butte Mine Site community in Cottage Grove, Oregon

The cooperative project was the first pilot for the Partners in Technical Assistance Program, and was launched in the London School, located near the Black Butte Mine Superfund site in rural Cottage Grove, about 70 miles south of the university. The EPA Office of Superfund Remediation and Technology Innovation initiated the technical assistance program in 2013 to help communities affected by Superfund sites understand technical information and to enable meaningful community involvement in the Superfund decision-making process.

During a Black Butte Mine community information session, London School principal Laurie Briggs requested that EPA create materials to teach students about the nearby abandoned mine, where mercury and other contamination from mine waste affect creeks that flow into the nearby Cottage Grove Lake Reservoir and the Coast Fork Willamette River.

"EPA has a strong commitment to ensure that communities living near Superfund sites are informed and have opportunities to meaningfully engage in EPA actions, to protect human health and the environment," said Alanna Conley, EPA Region 10 community involvement coordinator. "This is a model educational project and partnership with the university, London School, and EPA that brings together environmental health science, local history, and a Superfund site."

Members of the pilot program team at the London School include, from left, Diana Rohlman, Ph.D., with the university Superfund program; Conley; Dan Sudakin, Ph.D., of the Superfund program; Briggs; and Hirsch. Other members of the team are Corey Fisher and Molly Kile, Ph.D., of the Superfund program; Dreyfus; Kira Lynch, from EPA Region 10; and Richard Muza, Region 10 Black Butte Mine project manager. (Photo courtesy of Naomi Hirsch)

Putting environmental health into context

The educational package "Mercury, the Community, and Me" is available online as modules for K-8 teachers. The activities help connect students to the environment by defining environmental health, providing an overview of mercury and how it enters the environment and the food chain, and delivering information about mercury and human health. The resources include background information, presentations, worksheets, games, and team assignments.

Two videos are also part of the curriculum. One provides more information about the Black Butte Mine Superfund site, including its historical background. The other introduces students to careers in science, highlighting scientists from the university and EPA.

The activities in the educational package build upon prior work on the Hydroville project, a nine-week series to help high school students understand environmental health, developed through the university's Environmental Health Sciences Core Center.

Fostering collaboration and engaging stakeholders

"The PTAP [Partners in Technical Assistance Program] project provided a structure to build relationships with EPA Region 10 and impact a community living near a Superfund site," said Naomi Hirsch, the university Superfund program Research Translation Core coordinator. "The final products also included contributions from our SRP trainees. We hope the educational resources are models for other schools and future partnerships."

"The excellent work done by the university Superfund Research Program, in collaboration with EPA and the London School in Cottage Grove, demonstrates how the pilot program can bring expertise and resources into communities near Superfund sites to meet technical assistance needs and enhance overall community restoration and cleanup," Melissa Dreyfus, EPA lead for the pilot program.

(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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Town hall event explores ways to increase research funding

By Kristen Ryan

Students, faculty, and research professionals from local institutions gathered Sept. 2 at the Research Triangle Park headquarters in Durham, North Carolina, for the first public event organized by the newly reinstated North Carolina Triangle Chapter of the Society for Neuroscience. They met to discuss a growing concern over federal research funding and science policy. Representative David Price, D-N.C., was one of the speakers.

Farris is a member of the NIEHS Synaptic and Developmental Plasticity Group. She is one of several scientists from the Laboratory of Neurobiology and NTP who are members of the Triangle Chapter of the Society for Neuroscience. (Photo courtesy of Steve McCaw)

Shannon Farris, Ph.D., an NIEHS postdoc and chapter representative, led the effort this summer to bring back the Triangle chapter, which has rapidly grown to more than 100 members. "Reactivating the chapter will provide a central place for scientists and the community to come together, and an opportunity to inform the public and our legislators how neuroscience research benefits our society," she said.

Members represent area universities, including the University of North Carolina at Chapel Hill (UNC), North Carolina State University, and Duke University, as well as local research organizations, such as RTI International and the U.S. Environmental Protection Agency. Along with Farris, several other NIEHS and National Toxicology Program (NTP) faculty and postdocs involved with neuroscience research are members of the chapter, including President-elect Patricia Jensen, Ph.D., lead researcher at NIEHS, and Secretary-treasurer Mamta Behl, Ph.D., an NTP toxicologist, who were part of the organizing committee for the event.

Rezvani is a professor of psychiatry and behavioral sciences who studies alcohol and nicotine addiction at Duke. (Photo courtesy of Steve McCaw)

Communicating the value of scientific research

Chapter President Amir Rezvani, Ph.D., a professor at Duke University, introduced Price, who is a member of the U.S. House of Representatives Appropriations Committee, where he promotes funding for research. Price was named a Champion of Science in 2002 by the Science Coalition, and recognized as Legislator of the Year in 2011 by the Biotechnology Industry Organization.

In his speech, Price discussed his most recent amendment proposal to increase funds for the National Science Foundation for fiscal year 2015. Despite strong bipartisan support for biomedical research, the proposal was not adopted. "There is no clear way to pay for such increases, which speaks to a larger dilemma regarding the need for a comprehensive fiscal plan to balance the budget," he explained.

Edward Levin, Ph.D., Duke University professor of psychiatry and behavioral sciences, asked a question that was on the mind of many people at the event. "How can we get together with local and federal government to look at the long view of research in the RTP area?" (Photo courtesy of Steve McCaw)

After a lively question and answer period, the meeting concluded with a reception that allowed the audience to continue discussions about federal support for research and learn more about the Triangle Chapter of the Society for Neuroscience.

The importance of supporting scientific research will also be a main topic during an upcoming visit to NIEHS by Rep. Renee Ellmers, R-N.C., in October. The majority of NIEHS employees reside in the districts represented by Price and Ellmers.

(Kristen Ryan, Ph.D., is an Intramural Research Training Award fellow in the NTP Systems Toxicology Group.)

Price joined Triangle chapter members joined Price following the town hall meeting. Shown, from left, are Leah Townsend, a UNC doctoral student; Behl; Chintan Oza, Ph.D., a postdoctoral fellow at Duke University; Rezvani; Price; Farris; Charlotte Boettiger, Ph.D., an assistant professor at UNC; and Jensen. (Photo courtesy of Steve McCaw)

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University of Massachusetts junior faculty visit NIEHS to find a home for their research

By Joe Balintfy

A group of 10 junior faculty members from the University of Massachusetts at Amherst visited NIEHS Sept. 12 to get the basics on submitting grant applications and to discuss how their environmental health research fits with the institute's mission.

"We matched their research interests with the most relevant Program Office, so each visitor was able to get personalized advice from the program staff," said NIEHS Health Scientist Administrator Jerry Heindel, Ph.D. He added that NIEHS encourages researchers to speak with program officers about their plans, and to stop by when they are in the area. However, this visit was the first of its kind on this scale.

"Keep us informed of your successes and research findings on NIEHS supported projects because your success is our success," Collman requested of the visiting University of Massachusetts junior faculty. (Photo courtesy of Steve McCaw)

Insightful information from the institute

Led by Mary Fechner, Ph.D., of the university's Office of Research Development, and hosted by Heindel, the group met NIEHS senior leadership, including Deputy Director Richard Woychik, Ph.D., and Gwen Collman, Ph.D., director of the Division of Extramural Research and Training (DERT). The visitors toured NIEHS, heard presentations about the funding process, and had one-on-one meetings with the staff.

Collman gave specific tips about how to stay connected to NIEHS, advising the visitors to read the NIEHS strategic plan and the Environmental Factor newsletter; attend NIEHS workshops or events, including the council meetings, in person or by webcast; participate in webinars, for example, the Partnerships for Environmental Public Health, exposome, and inflammation series; and interact with NIEHS staff at meetings, such as the conferences hosted by the Society of Toxicologists and International Society of Environmental Epidemiologists.

"This visit was a way for new university staff to learn about NIEHS in general, and better understand the personnel and programs they should know about," said Heindel. (Photo courtesy of Steve McCaw)

Putting a face on the funding process

Assistant Professors from the university's School of Public Health Division of Environmental Health Sciences emphasized the value of the opportunity to talk with NIEHS program officers. "I was excited to be able to talk to people who can support my research and help me focus it so that it will be fundable," said Laura Vandenberg, Ph.D. "That's what we all care about."

"I made two applications last year, both for NIEHS grants, and I didn't receive any," commented Alexander Suvorov, Ph.D. "Now, I think that with a better understanding of the process, I will be able to do it."

The group was able to visit together as part of a career development program at the university, which had invited NIEHS staff to visit earlier this year.

(Joe Balintfy is a public affairs specialist in the NIEHS Office of Communications and Public Liaison.)

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"It's wonderful to have the chance for the scientists to go in-depth with their research to learn more about how this institute functions," said Fechner, far right. "It's one thing to read a website, but it's another thing to see how it all works." (Photo courtesy of Joe Balintfy)

Compatible mining to protect vulnerable populations and the environment

By Sara Mishamandani

The pace of mining exploration in Latin America has increased dramatically in recent decades. The Latin American Conference on Compatible Mining, supported by NIEHS, brought attendees from eight North and South American countries to San Luis Potosi, Mexico, to discuss and plan the future of compatible mining — a term coined at the conference.

Compatible mining is defined as the empowerment of communities, civilians, governments, and the private sector to collaborate in a way that minimizes and prevents the environmental and social impacts of mining. Talks at the meeting addressed large-scale and artisanal mining, environmental remediation, community impacts, community outreach, worker health, mining policy and decision making, and mining best practices. The University of Arizona Superfund Research Program, together with the university's Dean Carter Binational Center for Environmental Health Sciences, sponsored the Sept. 8-10 meeting.

The conference logo highlights the Pan-American map in the white cutout of the parrot wing, and includes the new term defined at the conference — mineria compatible, which translates to compatible mining. (Graphic courtesy of Fernando Diaz Barriga, Universidad Autonoma San Luis Potosi)

Compatible mining in policy and industry operations

The conference established the Pan-American Hub for Compatible Mining to promote best practices for mining operations and to protect human health, the environment, and local culture.. The Hub will enable networking among professionals and communities to identify and prioritize pressing issues in mining. A second meeting is planned for March 2016, in Peru.

"The concept of compatible mining is timely with the current pace of mining operations. [The University of Arizona Superfund Research Program], together with their collaborators, is well positioned to develop a hub of information exchange among the Americas," said Heather Henry, Ph.D., program administrator in the NIEHS Superfund Research Program. "The compatible mining hub exemplifies the NIEHS strategic goal to identify and respond to emerging environmental threats to human health, on both a local and global scale."

"Conference attendees discussed ways to facilitate transdisciplinary collaboration in research, information sharing, and capacity building," said Maier, right, shown here with Henry, center, and Mary Poulton, Ph.D., a professor in the University of Arizona Department of Mining and Geological Engineering. (Photo courtesy of Heather Henry)

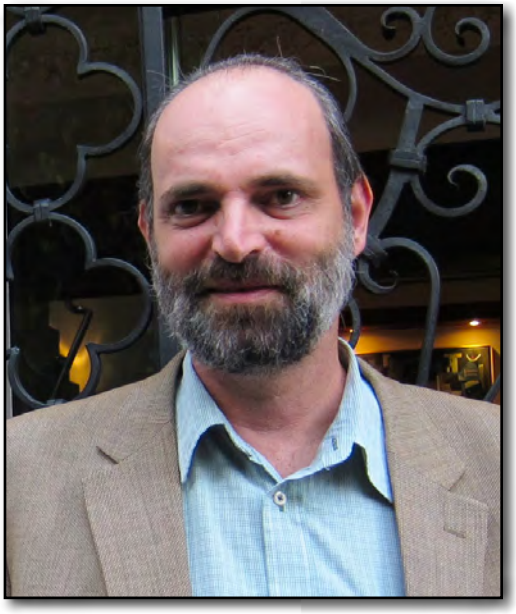
Putting the concepts into practice

In August, as planning for the meeting was underway, a mine wastewater spill contaminated rivers in Cananea, Mexico. Grupo Mexico, which owns the mine, contacted a group of researchers who collaborate through the U.S.-Mexico Binational Center and the University of Arizona Center for Environmentally Sustainable Mining, to evaluate the mid- and long-term impacts of the Cananea Mine spill.

Through collaborations with the Binational Center, the university's Superfund Research Program will work together with their Mexican colleagues. They will also perform metal analysis for the estimated 12,000 samples that will be generated by these studies. This group of investigators exemplifies the vision for the Pan-American Hub to bring together multiple stakeholders to achieve compatible mining. Grupo Mexico will support studies related to water, soil, and sediment contamination, biodiversity, and human health.

"Grupo Mexico recognizes what a disaster this is and wants us to help define the extent of the contamination now and follow what happens into the future," said Raina Maier, Ph.D., the university's Superfund Research Program center director and co-organizer of the meeting. "This team would not be in place and ready to respond if it were not for the NIEHS Superfund Research Program."

(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.)



Jim Field, Ph.D., director of the Dean Carter Binational Center and University of Arizona Superfund Research Program project co-leader, led the conference organizing effort. (Photo courtesy Raina Maier)

The group that will investigate the Cananea Mine spill includes professors and graduate students from the University of Arizona, the Universidad Nacional Autonoma de Mexico, Instituto Tecnologico de Sonora, and the Universidad de Sonora. (Photo courtesy of Raina Maier)

Conference attendees included representatives from industry, regulatory agencies, indigenous communities, nongovernmental organizations, and academia, as well as more than 100 students from the Autonomous University of San Luis Potosi. (Photo courtesy of Raina Maier)

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Clinical Feature

Coating carbon nanotubes reduces lung injury risk

By Ernie Hood

Experimental evidence from researchers around the world has shown that inhalation exposure to carbon nanotubes, which are one of the most commonly engineered nanomaterials, can cause chronic lung disease in animals that is similar to the fibrotic damage found in asbestos exposure. A series of collaborative experiments by NIEHS grantee James Bonner, Ph.D., and co-lead researcher Gregory Parsons, Ph.D., both of North Carolina State University, and the NIEHS Clinical Research Unit, has shown that coating multiwalled carbon nanotubes with thin layers of aluminum oxide, via a process called atomic layer deposition, reduces lung injury in both animal and cellular models.

Bonner, a longtime NIEHS grantee and collaborator, studies potential human health risks of emerging nanotechnologies, to support safe design. (Photo courtesy of Anna Bonner)

The collaborative study was a transdisciplinary effort that combined expertise in nanotoxicology by Bonner's team, nanoscale engineering by the Parsons Laboratory, and a human translational component provided by the NIEHS Clinical Research Unit.

Multiwalled carbon nanotubes are fiber-like, engineered graphene nanomaterials with a wide range of applications in engineering, electronics, and medicine. Human exposure to the nanotubes is inevitable because of their increasing production and use in a variety of consumer products. Recent studies shed light on potential risks to human health from exposures and support the safe design of materials that contain carbon nanotubes.

Coating works

In a paper published Sept. 12 in the journal PLOS One, researchers studied aluminum oxide coating via atomic layer deposition to determine whether it would alter the expression of pro-inflammatory and pro-fibrogenic cytokines, and whether the coating would alter the pro-fibrogenic potential in the lungs of mice, in response to exposure. Both *in vitro* and *in vivo* results showed that the coating significantly reduced lung fibrosis both in the cell and animal models, compared to uncoated nanotubes.

Asked whether it was likely that the study's findings would change manufacturing practices, Bonner explained that initial production probably would not be affected, but the results should provide some insight as to how post-manufacturing modifications, referred to as functionalization, change the potential of nanotubes to cause disease.

"The specific type of functionalization will more likely be driven by how well it improves the utility of the carbon nanotube for a specific product," he said. "The challenge for toxicologists will be to test the potential adverse human health effects of an increasing number and variety of functionalized engineered nanomaterials."

Breaking up helps

The study also showed that nanotube length is likely to be an important determinant of the inflammatory and fibrogenic effects of multiwalled carbon nanotubes in the animal lung. It is difficult for mammalian lungs to clear long fibers, such as asbestos, making them more persistent and more likely to cause fibrosis. Fortunately, coated nanotubes tend to break up in the lungs, and the resulting shorter fibers are likely to be cleared more rapidly than uncoated or thinly coated particles.

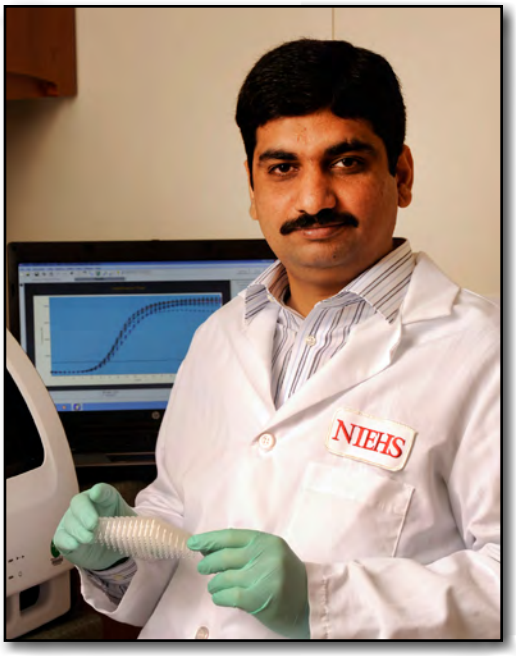
The NIEHS Clinical Research Unit collected the primary human monocytes used in the study from healthy adult volunteers, under a protocol approved by the NIEHS Institutional Review Board. "We were pleased to have an opportunity to collaborate directly with Dr. Bonner's group in this and the other studies we are jointly conducting," said Stavros Garantziotis, M.D., medical director of the Clinical Research Unit and acting clinical director.

"Dr. Garantziotis and Dr. Salik Hussain were instrumental in providing an important clinical translational component to the study by establishing that blood monocytes (white blood cells) from normal human donors had very similar responses compared to our immortalized human monocyte cell lines, when exposed to the carbon nanotubes modified by atomic layer deposition," Bonner said.

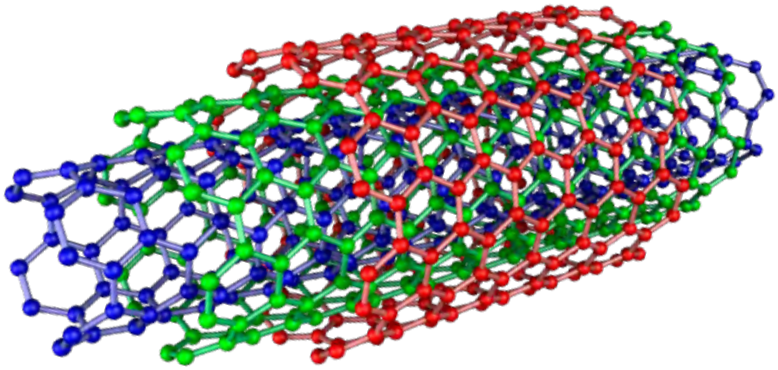
(Ernie Hood is a contract writer with the NIEHS Office of Communications and Public Liaison.)

Citation: Taylor AJ, McClure CD, Shipkowski KA, Thompson EA, Hussain S, Garantziotis S, Parsons GN, Bonner JC. 2014. Atomic layer deposition coating of carbon nanotubes with aluminum oxide alters pro-fibrogenic cytokine expression by human mononuclear phagocytes in vitro and reduces lung fibrosis in mice in vivo. PLoS One 9(9):e106870.

Garantziotis and Bonner have collaborated for several years on research exploring the health and safety risks associated with emerging nanoparticle technology. (Photo courtesy of Steve McCaw)



The Society of Toxicology recently named Salik Hussain, D.V.M., Ph.D., Outstanding Postdoctoral Fellow, Nanotoxicology Specialty Section. He is a visiting fellow with the NIEHS Office of Clinical Research and co-author of the study. (Photo courtesy of Steve McCaw)



Multiwalled carbon nanotubes are made of concentric layers of graphene rolled into a tubular shape and are currently used in conductive polymers and sporting goods. They show promise for applications in textiles and fibers, advanced ceramics, and medical implants. (Image by Eric Wieser (Own work) [CC-BY-SA-3.0 (http://creativecommons.org/licenses/by-sa/3.0)], via Wikimedia Commons)

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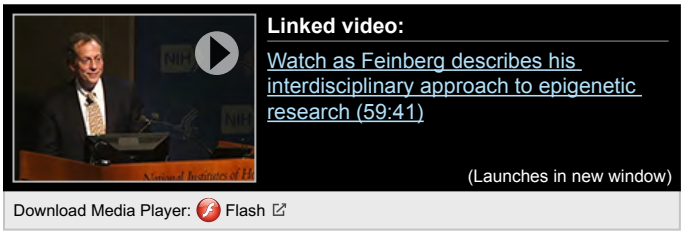
Science Notebook

NIEHS grantee kicks off high-profile lecture series at NIH

By Eddy Ball

NIEHS grantee Andrew Feinberg, M.D., was the featured speaker Sept. 3 at the opening talk in the 2014-2015 Wednesday Afternoon Lecture Series at the National Institutes of Health (NIH) in Bethesda, Maryland. He reported on developments in his NIEHS-supported research on "The Epigenetic Basis of Common Human Disease."



"He is, in fact, a remarkably creative scientist," Collins, above, said of Feinberg, who has synthesized insights from the fields of quantum physics, astronomy, and mathematics, as well as the humanities, with his biomedical training and research. (Photo courtesy of NIH)

Feinberg is the recipient of grants from several NIH institutes, but his lecture focused primarily on his NIEHS-administered funding for developing "A General Stochastic Epigenetic Model for Evolution, Development, and Disease," The grant is managed by health scientist administrator Lisa Chadwick, Ph.D.

In his introduction of Feinberg, NIH Director Francis Collins, M.D., Ph.D., commented on the speaker's long list of honors, including his distinguished professorships, membership in the Institute of Medicine, and selection as a 2011 NIH Director's Pioneer Award recipient.

Reflecting on his long relationship with Feinberg, dating back to their tenures as faculty members at the University of Michigan, Collins said, "I don't know exactly what Andy's going to put in front of you today, but I'm sure you'll find it to be interesting and provocative."

"You have to look at genetics and epigenetics together," Feinberg explained, through a series of examples of new insight achieved through integrated methodologies. (Photo courtesy of NIH)

The first part of Feinberg's lecture echoed what he presented at the February 2013 meeting of the NIEHS of the National Advisory Environmental Health Sciences Council (see story), of which he is now a member. The second half reported on subsequent work that points to newly discovered targets for possible therapeutic interventions.

Forging an integrated theory

Feinberg opened his talk with the question that drives his research — what shapes the observable characteristics of health and disease in individuals, or their phenotypes, resulting from the interaction of genes with the environment.

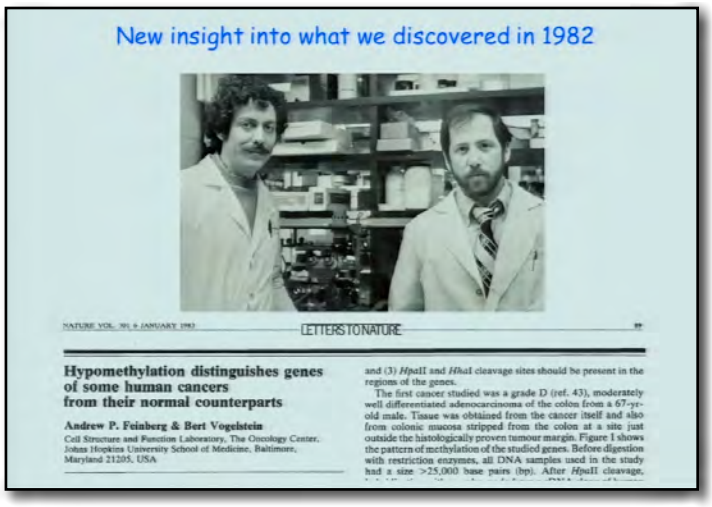
Referring to studies finding that genetics alone could explain no more than 20 percent of all disease, Feinberg looked beyond genetics to changes in gene expression that don't change DNA, but profoundly influence health and disease. "Our environment shapes, in a remarkable way, our phenotype, but not through the genes themselves, but through influencing how the epigenome might take place," he explained.

Around the turn of the century, Feinberg expanded his research beyond epigenetics and cancer, a connection well established by that time. "I became very interested in whether or not one could begin to explore the epigenetic basis of common disease, generally," he said, "particularly where environmental exposure might be important."

Exploring what he calls variably methylated regions, which are present in up to half of the genome, Feinberg has steadily refined a general stochastic, or random element, epigenetic model.

The model both explains how the degree of plasticity in defined regions can influence tissue-specific differences that are separate from DNA, which is consistent across tissues, a sort of inner organism process of selection — as well as natural selection on a species level consistent with a Darwinian model. He presented recent data on aging, rheumatoid arthritis, and diabetes-related obesity in support of the model.

Just as his model integrates evolution, development, and disease, Feinberg's group has combined methodologies and models, specifically comparative human and mouse tissue studies, for new insights.



With his Johns Hopkins mentor, Bert Vogelstein, M.D., Feinberg, left, reported the identification of DNA hypomethylation as a signature of cancer, in a landmark 1983 paper in Nature. In the course of three decades, his research has expanded dramatically in range and volume from that insight about cancer. (Photo courtesy of NIH)

More about the Pioneer Award and the Wednesday Afternoon Lecture Series

The NIH Director's Pioneer Award program provides grants from the NIH Common Fund for highly innovative approaches that have the potential to produce an unusually high impact on a broad area of biomedical or behavioral research. It complements traditional, researcher-initiated NIH grant programs, by supporting individual scientists of exceptional creativity.

Each year the Wednesday Afternoon Lecture Series features some of the biggest names in biomedical and behavioral research, nominated by the NIH community. This academic year's lineup includes 34 scientists from across the spectrum of biomedical research.

"The integration of epigenetic information with genetic sequence could reveal patterns related to human disease that we wouldn't know otherwise," he said. He pointed to newly discovered cases of distant regulation of the genome, identified by epigenetic analysis, by single nucleotide polymorphisms, which were revealed through genome-wide association studies.

Significantly, some of these patterns could lead to potential interventions. "I think that this might be a way to uncover new targets that are, if not the primary generators of these phenotypes, certainly mediators, and they're drugable. That is, we might be able to come up with compounds that can modify the phenotype," he concluded.

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Baden shares saga of translation — from toxin to treatment and prevention

By Audrey Pinto

For veteran NIEHS grantee Daniel Baden, Ph.D., a William R. Kenan Jr. distinguished professor of marine sciences and director of the Center for Marine Science at the University of North Carolina Wilmington, Aug. 31 was a noteworthy day. He presented the inaugural lecture in Duke Environment Hall, the new home of the Duke University Nicholas School of the Environment, opening the 2014 Integrated Toxicology and Environmental Health Program (ITEHP) lecture series with an inspiring account of research translation from bench to bedside to public health.

"Translational science is inherently interdisciplinary," Baden told the audience. He also observed that with climate change, the oceans are getting warmer and algal blooms thrive and multiply in warm waters. (Photo courtesy of Steve McCaw)

In his presentation, Baden shared the progress his team and collaborators worldwide have made to isolate new chemicals from *Karenia brevis (K. brevis)*, the dinoflagellate that produces the brevetoxins responsible for Florida red tide. He explained that nontoxic compounds isolated from the organism hold promise for countering the effects of red tide exposure, for treating cystic fibrosis, chronic obstructive pulmonary disease, and other forms of respiratory illness, as well as serving as a potential agent for drug delivery.

In many ways, Baden, with his long and productive relationship with NIEHS, reflects the vision and goals outlined in the NIEHS 2012-2017 strategic plan for innovative cross-disciplinary translational research.

Duke University professor Edward Levin, Ph.D., who directs the lecture series, introduced Baden and moderated the question-and-answer session following his talk. (Photo courtesy of Steve McCaw)

Serendipity at the bench

To illustrate how his team found this new therapeutic agent, Baden took the audience on a journey through scientific discovery, exploration, and the translation of research findings. He shared his belief that scientists must be open to new possibilities and that scientific discoveries should be applied to improving public health.

"We had a serendipitous moment when we found that one natural product from *K. brevis*, called brevenal, prevented, reduced, or reversed bronchoconstriction caused by other toxins from the same organism," he explained. "This was a baffling finding, but after several experiments, we confirmed that brevenal did indeed act as an antitoxin that also promoted mucociliary clearance, increased anti-inflammatory response, and promoted whole lung clearance."

In a public-private partnership, the team is now working with a pharmaceutical company to begin phase I trials, to move this new therapeutic into the Cystic Fibrosis Therapeutics pipeline, because of its potential to restore ion transport and to regulate mucus.

NIEHS health scientist administrator Annette Kirshner, Ph.D., center, was part of an audience that nearly filled the new auditorium. She was the program administrator for much of Baden's NIEHS-funded work when he was at the University of Miami. (Photo courtesy of Steve McCaw)

Transforming the mysteries of the ocean into marketplace miracles

"As our research progressed," Baden continued, "we found other therapeutic applications that have now been licensed. For example, brevisin — another polycyclic ether isolated from the dinoflagellate *K. brevis* — has no apparent toxicity and moves rapidly across membranes, including the blood brain barrier. This compound, trademarked Escortin, has huge importance for carrier-mediated chemotherapy, targeted drug delivery, and brain cancer."

Baden noted that brevenal has many more potential applications, including therapeutic and preventive agents that could be used in rescue packs for people at beaches, during red tide outbreaks, and for pretreatment. Through a compassionate use permit from the U.S. Food and Drug Administration, the Mote Marine Laboratory in Florida used brevenal to counter the toxic effects of red tide in manatees. The U.S. Department of Defense has also expressed interest in its inhaled mucociliary clearance properties.

Environment Hall was designed to meet or exceed the criteria for the U.S. Green Building Council's LEED platinum certification — the highest level of sustainability. (Photo courtesy of Steve McCaw)

The team continues its research into structure activity of the brevenal receptor, as reported in an NIEHS-funded paper published in March by the journal Marine Drugs. Work is also ongoing to streamline production of brevenal and brevisin, for trials of safety and efficacy, as well as clinical trials.

Baden concluded his presentation by reiterating the importance of opening our minds to new possibilities. "Our oceans are filled with scientific potential, renewable resources, and treasures yet to be tapped," he said.

Citation: Goodman A, McCall JR, Jacocks HM, Thompson A, Baden D, Abraham WM, Bourdelais A. 2014. Structure activity relationship of brevenal hydrazide derivatives. Mar Drugs 12(4):1839-1858.

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

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Data science holds the future of cutting-edge analyses

By Kelly Lenox and Eddy Ball

The growing priority of data science at NIEHS, to glean crucial insights from the vast amounts of information generated in biomedical research, was underscored by two September events. A two-day workshop Sept. 15-16 focused on progress toward a consistent language for environmental health research. It was followed by a Sept. 17 mini-symposium, which was co-sponsored by the NIEHS Data Science Seminar Series and Keystone Science Lecture Seminar Series.

Boyles encouraged audience interaction with speakers at the mini-symposium, fostering an energetic exchange. (Photo courtesy of Steve McCaw)

"Workshop for the Development of a Framework for Environmental Health Science Language" brought together an interdisciplinary group of experts at North Carolina State University (NCSU) in Raleigh. Chaired by Carolyn Mattingly, Ph.D., of NCSU, and Melissa Haendel, Ph.D., of Oregon Health and Science University, the workshop explored a framework for creating standard languages to ensure that descriptions and content of data sets can be understood by the broader research community.

Consistency in language and terminology is a crucial step toward enhancing reproducibility, data reuse, and data integration. The mini-symposium, held at NIEHS, highlighted several areas of research that have applied data science techniques to advance diagnosis and treatment of disease.

According to McCray, the variability and severity of ASD symptoms suggest that genotypic links may help tease out underlying conditions. (Photo courtesy of Steve McCaw)

Developing a common language

NIEHS and National Toxicology Program Director Linda Birnbaum, Ph.D., opened the workshop and introduced the major themes of the presentations that followed. "We really need to begin to integrate the huge amounts of data being generated," Birnbaum told the attendees. "A common language is very important, and we're going to have to be bold," she said, referring to the collaboration and knowledge management that are essential to the task.

Along with representatives of universities, agencies, and other organizations, a number of NIEHS scientists and grantees participated in the meeting. After two keynote presentations, 11 short talks, a panel discussion, and two breakout sessions, participants spent the remaining half-day drafting reports that will lead to a paper outlining plans to advance the effort toward a common language in environmental health science data.

But, as Haendel cautioned early in the workshop, that's just the first step. "Any ontology worth its salt is never done." Still, the workshop itself was a major leap forward for a working consortium that had humble beginnings with a local meeting in the summer of 2013 (see story).

"Data integration, regardless of any other implementation, is achieved by creating controlled vocabularies and ontologies," White said, emphasizing that it is a consortium-driven process. (Photo courtesy of Steve McCaw)

Data science advances underway

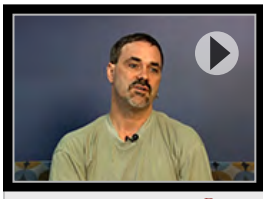
Becky Boyles, data scientist in the NIEHS Office of Scientific Information Management, opened the mini-symposium, which drew a full house. "It's the first data science mini-symposium we have sponsored," she said, "and we're very open to what people want to see in future seminars." Boyles was joined by Astrid Haugen, science program analyst with the NIEHS Division of Extramural Research and Training, who co-hosted the talks.

Three invited experts in data analysis focused on autism spectrum disorder (ASD), the microbiome, and model systems (see text boxes).

Alexa McCray, Ph.D., director for biomedical informatics at Harvard Medical School, presented her work modeling ASD. McCray and her team work with highly detailed phenotyping, or collecting clinical, biological, and other observable data. They have developed a set of consistent terms, or ontology, that enables researchers to integrate and query disparate ASD datasets.

Owen White, Ph.D., lead investigator for the data coordination and analysis center of the National Institutes of Health Human Microbiome Project, engaged the audience in an animated discussion of the importance of data science, by using the example of metagenomics, which is the effort to analyze the genomic data of humans and of the vast array of microbes involved in human metabolic functions.

According to Haendel, the benefits of data science advancements include searchable details on author contributions and useful details on resources — for example, a link to the genome of the mouse used in a study and links to other studies using the same strain. (Photo courtesy of Steve McCaw)



Linked video:

Watch as White explains the work at the Human Microbiome Project Data Analysis and Coordination Center in this University of Maryland video. (0:32)

(Launches in new window)

Download Media Player: Flash

Melissa Haendel, Ph.D., assistant professor in the Oregon Health and Science University library, highlighted another data science challenge with great promise. The Monarch Initiative is a translational research project that provides tools for navigating great stores of genetic and phenotypic data across species, to advance diagnosis and treatment of diseases that are rare or previously undiagnosed.

McCray — Data access to improve assessment of ASD

"An ontology is a way to characterize the world, taking concepts, as a thesaurus does, in order to understand relationships among them," McCray told the audience. "An ontology provides a structured, computable way of representing a domain of interest, such as ASD."

In addition to collecting biological samples for genetic data, researchers used a battery of scoring instruments on 500 families affected by ASD, including interviews, questionnaires, and direct clinical assessments. In the ontology, published in a 2013 paper, McCray's team developed various concept categories for different types of data. For example, the ontology's category of self-injurious behavior associates the frequency of head banging measured in one instrument with the frequency children hit themselves against an object, which was measured in another instrument.

According to McCray, use of the ontology, which is publicly available, will enable phenotypic data to be correlated with genome-wide association studies, in the hopes of finding genetic links for this highly heritable condition. Discovery of genotypes related to autism could lead to earlier diagnoses, enabling early interventions, which often have marked results.

Citation: McCray AT, Trevvett P, Frost HR. 2014. Modeling the autism spectrum disorder phenotype. Neuroinformatics. 12(2):291-305.

White — Microbiomes, metabolic pathways, and metagenomics

"There is more metabolism going on in your microbiome than in any other organ of your body, so it really functions as another organ," White said, opening his presentation. However, research may be hampered by databases that do not conform to a larger ontology or control vocabulary, or that omit metadata, such as whether a sample was collected from an individual who was healthy or ill. These shortcomings limit the usefulness of data queries by scientists, who might otherwise find information to further their research.

"Data integration is achieved by creating controlled vocabularies and ontologies," White said, referring to the importance of using key words people agree on, which he praised as a process of high scholarship.

White underscored the growing importance of data coordination centers, or curators, who regularize the data so it can be integrated. This will also allow scientists to compare studies that use different data sources.

Haendel — Using model systems to compare undiagnosed diseases

According to Haendel, numerous databases include disease and phenotype information, but it is difficult to make connections across the sources. Clinical data and the results of studies on model organisms, such as fish and mice, are available, but, as McCray noted with autism studies, phenotypic data are described in different terms across the sources.

"Constipation, in humans, is described as decreased gut peristalsis in zebrafish," Haendel noted. "Standardizing phenotypes is the final frontier and will enable us to compare phenotypic features of different species, so we can understand the underlying genotypes and environmental causes that give rise to them," she said.

Haendel and her colleagues built an ontology that connects anatomy ontologies to genotypes, incorporating the different genome data of each source. The resulting ontology, dubbed the Uberon, makes it possible to query all organisms in the system for a particular phenotype and return genotype data associated with it.

Haendel noted that integration of environmental exposure data is lagging further behind, due to the lack of standardized language — a challenge that the previous two-day workshop, which she co-chaired, helped move forward.

Citation: Mungall CJ, Torniai C, Gkoutos GV, Lewis SE, Haendel MA. 2012. Uberon, an integrative multi-species anatomy ontology. Genome Biol. 13(1):R5

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Trainee Barbara Nicol honored by Women Scientist Advisors

By Eddy Ball

Winning the National Institutes of Health (NIH) Fellows Award for Research Excellence (FARE) is a boost for any trainee's career, but for young female FARE winners, receiving an NIH Women Scientist Advisors Committee Scholar Award means being named one of the best of the best.

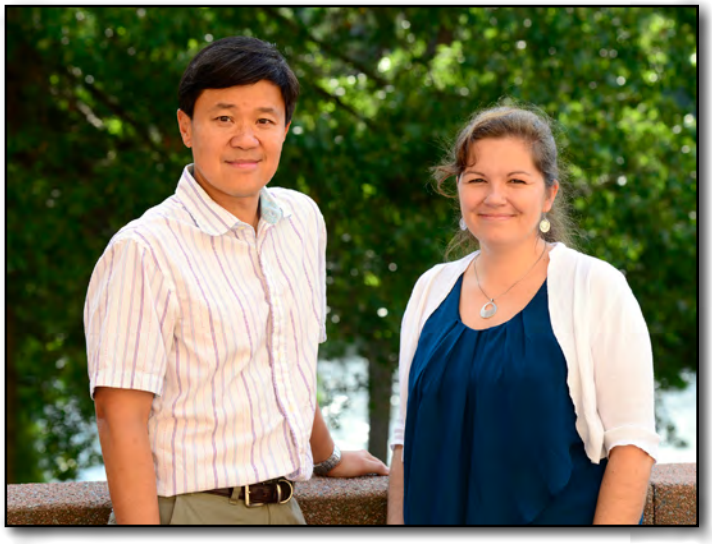
That's just what happened last month for NIEHS postdoctoral fellow Barbara Nicol, Ph.D., a member, since 2012, of the Reproductive Developmental Biology Group headed by Humphrey Yao, Ph.D. The advisors chose Nicol's FARE abstract, "Sox9/beta-catenin Double Knockout Mice Uncover a New Paradigm in Testis Differentiation" (see text box), as one of the three top studies, out of 113 young women scientist 2015 FARE winners.

Committee members put the FARE winners through a rigorous selection process. "Abstracts that were well written and told an interesting story rose to the top," wrote chair Judith Kassis, Ph.D. "We were very impressed with Barbara's abstract."

The advisors honor two to three female FARE award winners each year at the annual NIH Research Festival, and again at a Scholars Symposium in the spring, where awardees have the opportunity to present their research and meet with committee representatives and senior NIH leadership.

A select group of young scholars

Nicol joins former trainee Anne Lai, Ph.D., who won for her 2012 FARE study (see story), as part of the group of 12 committee scholars named since the award's initiation in 2010. NIEHS trainees have received a disproportionate number of the awards, rivaled only by the much larger National Cancer Institute and National Institute of Allergy and Infectious Diseases, which have also had two winners each.



Nicol, right, is one of several trainees in Yao's group who have been honored for their research in reproductive biology. In addition to Nicol, this year's FARE winners (see story) included another of Yao's postdocs, Erica Ungewitter, Ph.D., who also won last year. (Photo courtesy of Steve McCaw)

"I was really surprised," Nicol said modestly. "I've been here for just two years, and I feel that I've not done enough to earn this award… [And] there are so many bright postdocs here at NIEHS who are also FARE winners."

For his part, Yao was not at all surprised by Nicol's performance. "Barbara has been very creative, and this is not an easy project," he said. "She took it and made it into a very interesting story."

Yao emphasized the importance of this kind of competition for encouraging young women trainees to persist in their pursuit of scientific careers, a sentiment echoed by National Toxicology Program toxicologist Cynthia Rider, Ph.D.

Asking interesting questions about reproductive differentiation

Nicol's study stood out in large part because of its divergent approach to understanding the genetic defects that lead to sex reversal at birth or infertility, which are often the result of differentiation impairment of gonads during fetal life. Her findings shed new light on the complex antagonisms between pro-ovary and pro-testis pathways and challenge prevailing opinions about the role of specific proteins.

In her experiments, Nicol and Yao generated a genetic mouse model with the genes of pro-testis Sox9 and pro-ovary beta-catenin knocked out. Nicol compared differentiation outcomes, or phenotype, among male and female single knockout, double knockout, and wild type mice. Impaired phenotypes included partial and complete sex reversal.

In contrast to earlier studies, hypothesizing that testis differentiation was a result of a direct induction by Sox9, Nicol determined that the picture is more complex, requiring both Sox9–dependent and Sox9–independent morphogenetic changes. "This [finding] leads to a provocative hypothesis that in addition to stimulating Sox9 expression, Sry [the testis-determining gene] may also induce other unknown pro-testis genes," Nicol wrote.

Sex reversal phenotypes in humans can mean enormous human costs in terms of intersex anatomy and emotions. More research along the lines of Nicol's work could ultimately help scientists discover some way to intervene to improve the personal and reproductive lives of those affected by sex reversal.

"As one of the NIEHS representatives to the NIH-wide committee, I value the work that the committee does to bring awareness to the challenges that face women in science and to highlight the achievements of women throughout NIH," she wrote. "One such achievement that we are particularly proud of is that of Barbara Nicol, who was selected as a scholar out of a pool of talented women scientists."

Along with Nicol's selection, the advisors also presented scholar awards to trainees Bari Ballew, Ph.D., of the National Cancer Institute, and Christine Jao, Ph.D., of the National Institute of Diabetes and Digestive and Kidney Diseases.

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Advisory committee gives thumbs up to progress on alternative methods

By Ernie Hood

The Scientific Advisory Committee on Alternative Toxicological Methods gave an enthusiastic thumbs-up to the substantial reinvention launched last year by the groups it advises. The advisory committee met Sept. 16 at NIEHS to review work of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), and the National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Methods (see sidebar).

"It's been just over a year since ICCVAM released its new vision and strategic direction, which outlined a new plan and a new direction for the 15-member U.S. committee," said Linda Birnbaum, Ph.D., NIEHS and NTP director. "You're going to hear about some of the significant progress that has been made by the committee on a variety of fronts since the plan was adopted."

"These collaborations are exactly the type of activity that was envisioned when the ICCVAM Authorization Act was passed 15 years ago, and they will ultimately bring success in implementing methods to reduce, refine, and replace animals in toxicity testing," said Birnbaum. (Photo courtesy of Steve McCaw)

Fit-for-purpose approach

Perhaps most importantly, the coordinating committee has adopted an approach to validation of alternative test methods known as a fit-for-purpose approach. The method focuses on the needs of individual agencies and industries that are best positioned to quickly adopt a specific alternative test method.

Warren Casey, Ph.D., director of the interagency center, explained that the coordinating committee has evolved into more of a service organization. "Fit-for-purpose validation is really getting the right product to the right person at the right time, or getting the agencies what they need when they need it — high-quality results in a very short amount of time," he said.

Words have become deeds

Last year's good intentions formed the basis of this year's tangible accomplishments, making for action-oriented updates from the coordinating committee, the federal agencies that comprise the coordinating committee, the interagency center, and international alternative methods agencies, such as those in the European Union, Japan, Canada, and Korea. Several speakers noted that collaborations among agencies and other stakeholders have increased dramatically and substantial progress has been made toward acceptance of alternative methods.

As a key element of new vision and direction, the coordinating committee and interagency center increased engagement with the scientific community and stakeholders through focused workshops (see related story), webinars, and forums. Website upgrades have helped improve communication with stakeholders.

"We are very pleased with ICCVAM's new direction and its much stronger focus on achieving real reductions in animal use," said Patricia Bishop, People for the Ethical Treatment of Animals representative, echoing the positive sentiments expressed by many of the advisory committee members.

Finding alternatives to animal testing

The term alternative methods refers to methods of research and testing that use fewer or no animals, or that reduce animal pain and distress. The National Toxicology Program (NTP) participates in three committees that ensure the involvement of all stakeholders in the advancement of alternative testing methods.

- The **Interagency Coordinating Committee on the Validation of Alternative Methods** (ICCVAM) coordinates the activities of member federal agencies to replace, reduce, or refine animal use.
- The **NTP Interagency Center for the Evaluation of Alternative Methods** (NICEATM) supports ICCVAM activities and NTP high-throughput screening projects. The center conducts projects relevant to test method development, maintaining and promoting scientific quality and the protection of human and animal health and the environment.
- The **Scientific Advisory Committee on Alternative Toxicological Methods** (SACATM) advises NICEATM, ICCVAM, and the NIEHS and NTP director. Representatives are drawn from industries regulated by ICCVAM member agencies, animal welfare organizations, academia, test method developers, and regulatory agencies outside of the federal government.

"The level of collaboration we're experiencing is unprecedented in the history of ICCVAM," said Casey, "and, most projects we're trying to do within one year." (Photo courtesy of Steve McCaw)

"ICCVAM has accomplished multiple positive results, helping reduce the number of animals [used] in the process of meeting regulatory requirements for product registration," said outgoing advisory committee member Ricardo Ochoa, D.V.M., Ph.D., president of Pre-Clinical Safety Inc., reflecting on the progress made during his term. (Photo courtesy of Steve McCaw)

Won Keun Seong, Ph.D., is director of the Korean Center for the Validation of Alternative Methods, an international partner of the coordinating committee. (Photo courtesy of Steve McCaw)

"We think skin sensitization is one of the best areas we have for replacement of animal tests," said Joanna Matheson, Ph.D., of the U.S. Consumer Product Safety Commission and member of the Skin Sensitization Working Group. (Photo courtesy of Steve McCaw)

Advisory committee chair Daniel Wilson, Ph.D., of The Dow Chemical Company, summarized the sessions, indicating that ICCVAM has seen resounding success in the efforts it has championed in a remarkably short period of time. (Photo courtesy of Steve McCaw)

World Congress strengthens international ties

By Catherine Sprankle

NICEATM and ICCVAM strengthened international ties Aug. 24-28 at the Ninth World Congress on Alternatives and Animal Use in the Life Sciences in Prague.

- NICEATM staff helped organize a satellite meeting, "Workshop on Alternatives to the HIST for Acellular Pertussis Vaccines: Progress and Challenges in the Replacement of HIST."
- Casey co-chaired the Activity Updates From International Validation Centers session and summarized NICEATM and ICCVAM activities.
- NICEATM contractor Nicole Kleinstreuer, Ph.D., gave two presentations — one on an adverse outcome pathway for vascular development toxicity, and another on using high-throughput screening methods to identify endocrine disruptors.
- Raymond Tice, Ph.D., of NTP, co-chaired two sessions — Updates on Research Activities from the USA, and High-throughput Screening Models. He also presented updates on Tox21 activities.
- Abigail Jacobs, Ph.D., ICCVAM co-chair, with FDA, co-chaired the Topical Toxicity-Phototox session. She also gave a presentation on internationally harmonized nonanimal approaches to photosafety testing.
- Suzanne Fitzpatrick, Ph.D., with FDA, co-chaired and gave a presentation at the Tissues and Organs-on-a-Chip session. She also presented the regulatory perspective on adverse outcome pathways, and a process for international cooperation on regulatory science.
- Richard McFarland, Ph.D., with FDA, discussed reducing, refining, and replacing animal use in preclinical testing of cellular and gene therapies.
- Staff from NICEATM and the NTP Biomolecular Screening Branch prepared and presented eleven scientific posters.

A mild, late summer day was the perfect opportunity to collect the committee members and attendees outdoors for a group photo. (Photo courtesy of Steve McCaw)

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

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Adverse outcome pathway workshop generates enthusiasm and collaboration

By Catherine Sprankle

A workshop Sept. 3-5 at the National Institutes of Health (NIH) in Bethesda, Maryland, brought together scientists from 21 countries, representing industry, academia, regulatory agencies, and special interest groups. The workshop, Adverse Outcome Pathways: From Research to Regulation, considered how the adverse outcome pathway concept could improve regulatory assessments of chemical toxicity. The National Toxicology Program Interagency Center for the Evaluation of Alternative Methods (NICEATM) co-sponsored the workshop with the nonprofit Physicians Committee for Responsible Medicine.

An adverse outcome pathway organizes existing knowledge on chemical mode of action, for example, from an initiating event such as receptor binding, through key processes, and ending with an adverse outcome such as disease or toxicity.

At the opening session, Austin related the adverse outcome pathways concept to research translation, which is the process of turning laboratory observations into interventions that improve the health of individuals and the public. (Photo courtesy of Catherine Sprankle)

The workshop featured plenary presentations, as well as breakout sessions to consider adverse outcome pathway applications, development of new pathways, and challenges to their adoption. Participants appreciated the collaborations and enthusiasm that the workshop generated, and the closing session emphasized the need to maintain that momentum.

Better understanding and practical applications

In his opening remarks, Christopher Austin, M.D., head of the NIH National Center for Advancing Translational Sciences, characterized the process of predicting toxicity as a grand challenge. "Traditionally we have exposed animals or humans and waited for the outcome at the other end, without understanding what goes on in between," he said. "This limits our understanding of mechanisms by which these things happen."

In addition to supporting a better understanding of how disease develops after chemical exposure, adverse outcome pathways help identify where more research is needed to understand underlying mechanisms, aid in chemical classification and prioritization for future testing, and guide the development of new testing approaches that use fewer or no animals.

Two well-received presentations demonstrated online tools for developing and sharing pathways. Stephen Edwards, Ph.D., of the U.S. Environmental Protection Agency, previewed a new wiki launched in September by the Organisation for Economic Co-operation and Development. Hristo Aladjov, Ph.D., a consultant at the Organisation, demonstrated Effectopedia, an online data collection and collaboration tool for delineating pathways. "I really appreciated the Effectopedia demonstration," commented one attendee. "I want to download it as soon as I get home!"

Participants look forward

"I don't think I've ever seen this much energy associated with a workshop," noted Warren Casey, director of NICEATM, which committed to establishing and managing an email list to keep attendees informed of related activities.

Presentations and links to webcasts from the workshop will be posted, and a workshop report will be published early next year.

Nicole Kleinstreuer, Ph.D., left, a contractor for NICEATM, and Kristie Sullivan, director of regulatory testing issues for the Physicians Committee for Responsible Medicine, co-chaired the workshop steering committee. (Photo courtesy of Catherine Sprankle)

During the poster session, Zhoumeng Lin, Ph.D., of Kansas State University, discussed his study on the effects of short-term atrazine exposure with Jessica Helm, Ph.D., of the Silent Spring Institute. (Photo courtesy of Catherine Sprankle)

Aladjov answered questions during the closing session. (Photo courtesy of Catherine Sprankle)

Finding alternatives to animal testing

The term alternative methods refers to methods of research and testing that use fewer or no animals, or that reduce animal pain and distress. The National Toxicology Program (NTP) is involved in three committees that ensure the involvement of all stakeholders in the advancement of alternative testing methods.

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(Catherine Sprankle is a communications specialist for ILS, the contractor supporting NICEATM.)

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TSPO — a biomarker of brain injury and inflammation

By Tara Ann Cartwright

Tomas Guilarte, Ph.D., addressed NIEHS scientists Sept. 10 as part of the Inflammation Faculty Seminar Series. Guilarte's talk, "TSPO: A Biomarker of Injury and Inflammation in the Brain and in Other Organ Systems," addressed the potential of translocator protein (TSPO) to indicate inflammation in organs. The protein is a known biomarker of brain inflammation and can be detected through noninvasive testing.

The Inflammation Faculty was organized following the NIEHS 2012-2017 Strategic Plan, which designated inflammation as one of six high-priority areas of focus across the institute (see story). Guilarte's seminar was co-hosted by Inflammation Faculty members Mamta Behl, Ph.D., toxicologist in the NIEHS Systems Toxicology Group, and Andrew Rooney, Ph.D., deputy director of the National Toxicology Program (NTP) Office of Health Assessment and Translation and co-coordinator of the group.

Guilarte is a member of the National Advisory Environmental Health Sciences Council (see story), serves as the deputy director of the NIEHS Center for Environmental Health in Northern Manhattan, and is an adjunct professor in the Department of Radiology at John's Hopkins Hospital. (Photo courtesy of Steve McCaw)

Both Behl and Rooney were intrigued by Guilarte's research, because of the potential use of TSPO as a marker of inflammation caused by exposure to environmental chemicals. "TSPO is an exceptional biomarker of brain injury, which may have potential for assessing inflammatory damage in multiple organ systems," Rooney said.

TSPO detectable with PET scan

Guilarte is a longtime NIEHS grantee and professor and chair of the Department of Environmental Health Sciences at the Columbia University Mailman School of Public Health. He and his team have successfully developed and validated TSPO as a clinical biomarker for brain injury and neurodegeneration. The protein is involved in the translocation of cholesterol from the outer to the inner mitochondrial membrane, a prerequisite for steroid synthesis. Under normal physiological conditions, expression of the protein in the brain is relatively low. However, when cerebral inflammation is triggered by brain injury, TSPO expression increases markedly in activated glial cells, especially in the microglia and astrocytes.

TSPO levels can be detected *in vivo* by positron emission tomography (PET), thus providing researchers such as Guilarte with a real-time picture of where inflammation caused by injury occurs in humans. Guilarte has also demonstrated that following neurotoxicant exposure, TSPO expression is selectively upregulated in damaged rodent brain regions.

Potential biomarker for inflammation in other organs

These brain studies led Guilarte to ask if TPSO could be used to examine inflammation in other organ systems, such as the heart. In recent studies, he demonstrated that TSPO expression was increased in the hearts of male mice and in men with myocarditis compared with women, due to testosterone.

To date, little is known about the function of TSPO in glial or peripheral cells, nor is there an explanation of why TSPO expression is upregulated during inflammation. However, Guilarte has evidence to suggest that it may be related to oxidative stress.

Rooney explained that TSPO is produced in both monocytes and macrophages outside the brain, which may explain why it is associated with inflammation. (Photo courtesy of Steve McCaw)

Chris McPherson, Ph.D., a biologist in the NTP Neurotoxicology Group, is interested in the effects of inflammation on neurogenic self-repair in the brain. (Photo courtesy of Steve McCaw)

Michael Fessler, M.D., lead investigator in the NIEHS Clinical Investigation of Host Defense Group, recently published a study on the connection between a cholesterol-controlling gene and increased inflammation. (Photo courtesy of Steve McCaw)

As he concluded his talk, Guilarte described an agenda for using both cell sorting and flow cytometry to examine TSPO expression in normal peripheral blood cells and in other disease states that exhibit inflammation.

(Tara Ann Cartwright, Ph.D., is a former postdoctoral fellow in the NIEHS Intracellular Regulation Group).

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NIEHS scientists consider the future of mammalian reproduction

By Shannon Whirledge

Twelve NIEHS scientists set out for Colby Sawyer College in New London, New Hampshire, Aug. 10-15 for the inaugural Gordon Research Conference on Mammalian Reproduction. The organizing committee acknowledged the outstanding work of NIEHS scientists, through invited talks and travel awards (see sidebar). The meeting embraced the heritage of the Gordon conferences, by featuring unpublished, up-to-the-minute findings and presentations by young researchers, including three NIEHS trainees.

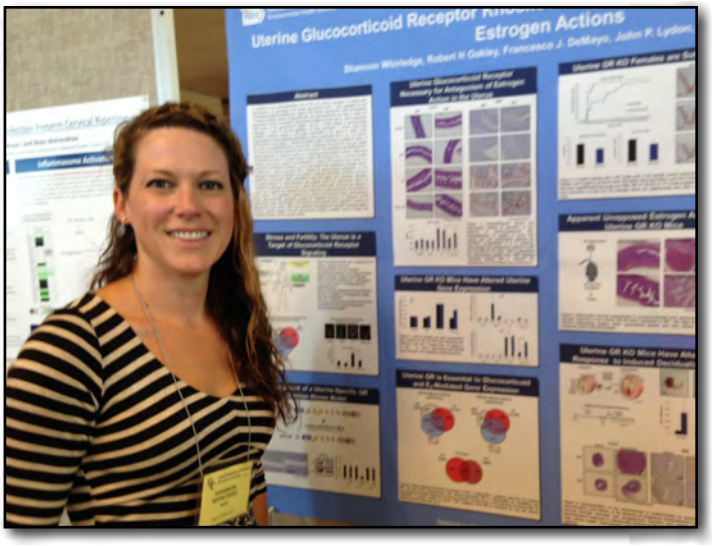
Williams and Liu appreciated the time to discuss science during one of the poster sessions. Liu felt he benefitted from the conference. "It allowed intimate interaction with big names in the field," he said. (Photo courtesy Sylvia Hewitt)

If exciting new data is a commodity, then the Gordon Research Conferences have cornered the market. With an emphasis on novel work, this year's Mammalian Reproduction conference filled five days with seminars, short talks, and poster sessions, and plenty of time for interacting with colleagues. The conferences have a long-standing history of hosting high-quality meetings that bring young scientists together to discuss current research.

NIEHS trainees recognize this as an advantage to attending the Gordon conferences. "These conferences are great for trainees to interact with senior scientists in the field," said Wipawee (Joy) Winuthayanon, Ph.D., a research fellow in the Receptor Biology Group. "The Mammalian Reproduction conference is small and interactive, with a lot of opportunities for social interactions with senior researchers," said Erica Ungewitter, Ph.D., Intramural Research Training Award fellow in the Reproductive Developmental Biology Group.

Sylvia Hewitt, senior biologist in the Receptor Biology Group, spoke of the unparalleled access to preeminent scientists. "It allows us to get input on projects that are under development from experts in the field, including learning techniques that will advance our research," she said.

During a coffee break, Donna Baird, Ph.D., left, lead researcher in the Women's Health Group, Ungewitter, center, and Winuthayanon reflected on the previous session. (Photo courtesy Sylvia Hewitt)



In addition to presenting an invited talk, Whirledge presented a poster, allowing the opportunity to receive substantial feedback and helpful insights for ongoing projects. (Photo courtesy Sylvia Hewitt)

Session talks by NIEHS researchers

- **Humphrey Yao, Ph.D.** — "Plasticity of the Somatic Cells in the Testis"
- **Carmen Williams, M.D., Ph.D.** — "Neonatal Estrogens Reprogram Female Reproductive Tract Function: Genome-Wide Approaches to Determine Underlying Mechanisms"

Short talks by NIEHS trainees

- **Erica Ungewitter, Ph.D.** — "GLI-Similar 3 Is a Master Regulator of Retrotransposon Silencing in Male Fetal Germ Cells"
- **Shannon Whirledge, Ph.D.** — "Uterine Glucocorticoid Receptor Knockout Mice Are Subfertile and Have Aberrant Estrogen Actions"
- **Miranda Bernhardt, Ph.D.,** Intramural Research Training Award fellow in the Reproductive Medicine Group — "Ca2plus Store Accumulation in Mouse Eggs Is Impaired by T-type Channel Inhibition Not by Loss of STIM1"

*The three trainees above, as well as Alisa Suen, predoctoral fellow in the Reproductive Medicine Group, and Chang Liu, predoctoral fellow in the Reproductive Developmental Biology Group, received travel awards to to attend the conference.

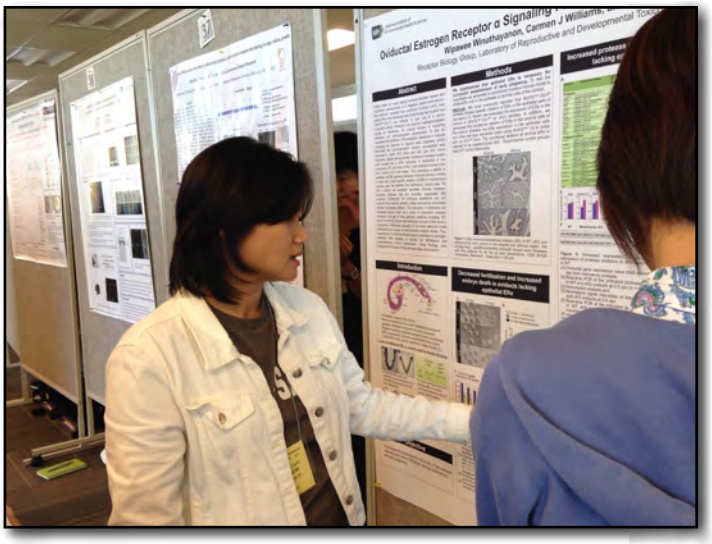
Clinical applications of NIEHS discoveries

The theme of this year's conference was "Translating Basic Science Into Clinical Applications." Sessions focused on innovative basic research findings that have implications for new clinical applications. The various mechanisms by which environmental compounds can disrupt normal reproductive functions are of considerable interest to NIEHS researchers and the entire field of reproductive biology.

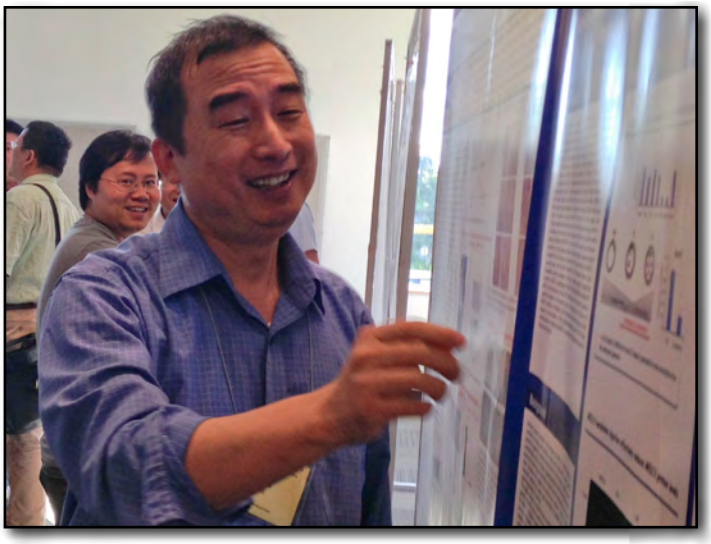
Humphrey Yao, Ph.D., lead researcher of the Reproductive Developmental Biology Group, was featured during the opening session. His talk focused on understanding the early events that lead to sex determination. Yao described data from a project he called his pet project, which uses genetic approaches to identify novel factors controlling development. Such insights can lead to a better understanding of the origins of infertility, according to Yao.

Carmen Williams, M.D., Ph.D., lead researcher of the Reproductive Medicine Group, spoke on "Environmental Effects on Reproductive Functions." She described how timing and the type of early-life exposure to endocrine disruptors can alter the development of disease in adults. The effects of diethylstilbestrol have persisted across generations and have resulted in infertility. Williams illustrated gene-specific epigenetic reprogramming that may be responsible for the transgenerational inheritance.

(Shannon Whirledge, Ph.D., is a research fellow in the NIEHS Laboratory of Signal Transduction.)



Winuthayanon, left, remarked that informal discussions during the sessions allowed her to set up possible future collaborations with other trainees. (Photo courtesy Sylvia Hewitt)



Yingpei Zhang, Ph.D., a biologist in the Reproductive Medicine Group, explained his work to interested conference attendees during his poster session. (Photo courtesy Sylvia Hewitt)

Yao took in the beautiful New England surroundings. The conference schedule included an afternoon hike up Mt. Kearsarge, elevation 2,936 ft. (Photo courtesy Sylvia Hewitt)

Shown from left, Liu, Baird, Suen, Bernhardt, Yao, Hewitt, Whirledge, Winuthayanon, Ungewitter, Barbara Nicol, Ph.D., a visiting fellow in the NIEHS Reproductive Developmental Biology Group, Zhang, and Williams savored the famous Gordon conference Thursday night lobster dinner. (Photo courtesy Sylvia Hewitt)

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This Month in EHP

The October issue of Environmental Health Perspectives (EHP) explores advances in remote-sensing technology and ways to inform risk perception with scientific evidence.

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Looking forward to the potential of remote-sensing technology

Scientists and government agencies worldwide already use satellite data to monitor air pollutants, infectious disease epidemics, harmful algal blooms, climate change, and more. But that's only the beginning of what we can do with remote-sensing technology.

Making wiser choices about risk

Whether in a regulatory or research setting, risk assessment typically entails a four-step process — hazard identification, hazard characterization, exposure assessment, and risk characterization. Individuals mentally assess risk in a similar way, but risk perception is shaped by several largely unconscious emotional processes shared by scientists and nonscientists alike.

Featured research and related news articles this month include:

- **Neurodevelopmental Disorders and Prenatal Residential Proximity to Agricultural Pesticides: The CHARGE Study** — Pesticides and Autism Spectrum Disorders: New Findings From the CHARGE Study
- **Residential Greenness and Birth Outcomes: Evaluating the Influence of Spatially Correlated Built-Environment Factors** — Beyond Spatial Relationships: Residential Greenness and Birth Outcomes
- **Residential Levels of Polybrominated Diphenyl Ethers and Risk of Childhood Acute Lymphoblastic Leukemia in California** — Zeroing In on a Risk Factor? PBDE Exposure and Acute Lymphoblastic Leukemia
- **The Navigation Guide (four-paper set)** — The Navigation Guide: Systematic Review for the Environmental Health Sciences
  - The Navigation Guide Systematic Review Methodology — A Rigorous and Transparent Method for Translating Environmental Health Science Into Better Health Outcomes
  - The Navigation Guide — Evidence-Based Medicine Meets Environmental Health: Systematic Review of Nonhuman Evidence for PFOA (Perfluorooctanoic acid) Effects on Fetal Growth
  - The Navigation Guide — Evidence-Based Medicine Meets Environmental Health: Systematic Review of Human Evidence for PFOA Effects on Fetal Growth
  - The Navigation Guide — Evidence-Based Medicine Meets Environmental Health: Integration of Animal and Human Evidence for PFOA Effects on Fetal Growth

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Distinguished Lecture Series to feature Thomas Platts-Mills

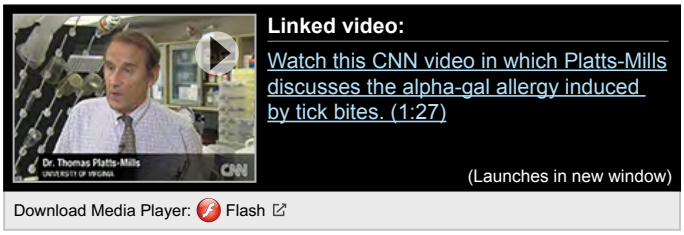
By Suchandra Bhattacharjee

Renowned allergist Thomas Platts-Mills, M.D., Ph.D., will present the next NIEHS distinguished lecture Oct. 14 at 11:00 a.m. in Rodbell Auditorium. The talk, "Epidemics of Allergic Disease 1870–2010: Hay Fever, Asthma, Peanut Allergy, and Now Delayed Anaphylaxis to Red Meat," will be hosted by Geoffrey Mueller, Ph.D., staff scientist in the NIEHS Nuclear Magnetic Resonance Group.

Platts-Mills began studying the connection between tick bites and allergic reactions after researching sensitivities to the cancer drug cetuximab, which contains alpha-gal. (Photo courtesy University of Virginia)

Chief of the Division of Asthma, Allergy, and Immunology at the University of Virginia School of Medicine, Platts-Mills is also a past president of the American Academy of Allergy, Asthma, and Immunology. "Dr. Platts-Mills has a towering status in the allergy community that is equally matched by his personality and physical stature," said Mueller.

Platts-Mills has pointed out that dust mite feces contain a potent allergen and can play a causal role in development of asthma. He was instrumental in determining that lone star ticks can induce an allergy to red meat. After receiving a tick bite, a person's antibodies to the alpha-gal carbohydrate, which is found in red meat, may rise. Patients with allergies to the carbohydrate have reported effects that occur three to six hours after eating beef, pork, or lamb. By comparison, allergic reactions to most other foods are instantaneous.



Among his many accomplishments, Platts-Mills has published hundreds of peer-reviewed articles, which are cited frequently, and has presented invited lectures and interviews worldwide. He is the first allergist to be named a Fellow of the Royal Society, the U.K. equivalent of the National Academy of Sciences. Also, his work has been featured in newspapers and media outlets, including The Wall Street Journal, "People's Pharmacy," ABC, NPR, CNN, "ScienceNOW," and Discover magazine.

(Suchandra Bhattacharjee, Ph.D., is a special volunteer in the NIEHS Free Radical Metabolism Group)

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Extramural papers of the month

By Nancy Lamontagne

- DNA methylation maps of early embryo development
- Perinatal lead exposure linked to obesity
- Oxidative stress predicts hip fracture
- AhR controls endotoxin tolerance pathway

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

DNA methylation maps of early embryo development

Researchers funded in part by NIEHS used high-throughput sequencing to produce genome-scale maps of DNA methylation at several developmental stages of early embryo development. This work is one step toward understanding the role of embryonic methylation patterns in normal development and disease.

Epigenetic modifications, including DNA methylation, affect gene expression without changing the genetic code. DNA methylation is drastically reprogrammed during early embryonic development in mice, but this reprogramming has not been well studied in humans. The new methylation maps confirm that global methylation patterns in human embryos closely resemble those of mice.

The researchers showed that there is considerable loss of methylation across most of the human genome just after fertilization and that methylation rapidly increases after implantation. One of the species differences researchers identified was that maternally contributed methylation is targeted to species-specific sets of CpG island promoters that extend beyond DNA regions known to control genes which are preferentially expressed from one parental chromosome.

Citation: Smith ZD, Chan MM, Humm KC, Karnik R, Mekhoubad S, Regev A, Eggan K, Meissner A. 2014. DNA methylation dynamics of the human preimplantation embryo. Nature 511(7511):611-615.

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Perinatal lead exposure linked to obesity

NIEHS grantees report that perinatal lead exposure is associated with obesity, even at low levels. The data support the hypothesis that toxicant exposures in the womb can contribute to higher risk for obesity later in life.

To assess the effects of prenatal and early-life exposure to multiple physiologically relevant levels of lead, groups of female mice were exposed to lead in drinking water for two weeks before mating, and then throughout pregnancy and nursing. Groups of mice were exposed to lead concentrations of 2.1 parts per million (ppm), 16 ppm, and 32 ppm. The control group was not exposed. For the exposed groups, maternal blood lead levels tested at weaning were 4.1 (+/-1.3) micrograms per deciliter, 25.1 (+/-7.3) micrograms per deciliter, and 32.1 (+/-11.4) micrograms per deciliter, respectively.

Both female and male offspring with perinatal lead exposure showed increased energy expenditure compared to controls ($p<0.0001$ for both), and exposed female offspring had higher average activity compared to controls throughout their lives. Overall, food consumption increased in exposed males and females ($p<0.0001$ and $p<0.0008$, respectively), with significant linear trends at 6 months in males ($p<0.01$) and 9 months in females ($p=0.01$). The researchers also observed significant increases in body weight for males with medium and high exposures ($p=0.001$ and $p=0.006$), and significantly increased insulin response in males with medium levels of exposure ($p<0.05$).

The researchers conclude that perinatal lead exposure at maternal blood lead levels between 4.1 and 32 micrograms per deciliter is associated with increases in food consumption in offspring, bringing about increased body weight, as well as changes in energy expenditure, activity, glucose tolerance, and insulin response.

Citation: Faulk C, Barks A, Sanchez BN, Zhang Z, Anderson OS, Peterson KE, Dolinoy DC. 2014. Perinatal lead (Pb) exposure results in sex-specific effects on food intake, fat, weight, and insulin response across the murine life-course. PLoS One 9(8):e104273.

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Oxidative stress predicts hip fracture

An NIEHS grantee and colleagues report that biomarkers of oxidative stress are associated with hip fracture in postmenopausal women. If additional studies confirm these results, the biomarkers could help improve prediction of hip fracture, which is associated with substantial cost and a high risk of disability and death.

Oxidative stress occurs when the body insufficiently responds to reactive oxygen species. Environmental factors, such as radiation and pollutants, can add to the natural level of reactive oxygen species and overcome the body's defenses. Studies in people have suggested that oxidative stress might be a risk factor for osteoporosis, but its relationship with fracture risk was poorly understood. To find out more, the researchers prospectively assessed oxidative stress by measuring fluorescent oxidation products (FlOP) in 996 women from the Nurses' Health Study, who were 60 or older at baseline blood collection between 1989 and 1990. FlOPs are markers of global oxidation burden and can be measured using a fluorescent spectrophotometer.

The researchers measured plasma FlOPs at three excitation/emission wavelengths (360/420 nm, 320/420 nm, and 400/475 nm), reflecting products from different oxidative stress pathways. Women in the upper 30 percent of FlOP levels, measured at 320/420 nm, had 2.67 times the risk of hip fractures compared to those in the bottom 30 percent. No significant association was found between hip fracture and 360/420 nm or 400/475 nm FIOP measurements. Because FlOPs at 320/420 nm are generated when oxidative products react with DNA in the presence of metals, their strong association with hip fractures might reflect the coexisting effects of reactive oxygen species and heavy metals.

Citation: Yang S, Feskanich D, Willett WC, Eliassen AH, Wu T. 2014. Association between global biomarkers of oxidative stress and hip fracture in postmenopausal women: a prospective study. J Bone Miner Res; doi:10.1002/jbmr.2302 [Online 23 Jun 2014].

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AhR controls endotoxin tolerance pathway

Research by an NIEHS grantee and colleagues reports new details regarding the mechanisms involved in endotoxin tolerance, a phenomenon in which prior exposure to endotoxin from gram-negative bacteria reduces the host's inflammatory response to subsequent exposure. The findings could lead to new approaches for treating infectious diseases, by controlling host-pathogen interactions.

Although endotoxin-induced inflammation is necessary for fighting gram-negative bacteria, too much inflammation can cause damage and lead to sepsis. Endotoxin tolerance helps reduce overexuberant inflammation, but its underlying mechanisms are not well understood. The researchers used genetically modified mice to investigate the biological pathways involved in endotoxin tolerance. They found that primary exposure of mice to lipopolysaccharide activated the aryl hydrocarbon receptor (AhR) transcription factor and the liver enzyme tryptophan 2,3-dioxygenase. However, when the mice were again exposed to lipopolysaccharide, AhR engaged in long-term regulation of systemic inflammation, only when indoleamine 2,3-dioxygenase 1 was present. The resulting endotoxin tolerance protected the mice against immune response damage to both gram-negative and gram-positive infections.

The AhR receptor is also known to regulate toxic and biological effects of exogenous chemicals, and these new results point to a role for the receptor in contributing to host fitness.

Citation: Bessede A, Gargaro M, Pallotta MT, Matino D, Servillo G, Brunacci C, Bicciato S, Mazza EM, Macchiarulo A, Vacca C, Iannitti R, Tissi L, Volpi C, Belladonna ML, Orabona C, Bianchi R, Lanz TV, Platten M, Della Fazia MA, Piobbico D, Zelante T, Funakoshi H, Nakamura T, Gilot D, Denison MS, Guillemin GJ, DuHadaway JB, Prendergast GC, Metz R, Geffard M, Boon L, Pirro M, Iorio A, Veyret B, Romani L, Grohmann U, Fallarino F, Puccetti P. 2014. Aryl hydrocarbon receptor control of a disease tolerance defence pathway. Nature 511(7508):184-190.

(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 Raj Gosavi, John House, Mallikarjuna Metukuri, Simone Otto, and Shannon Whirledge

- NTP involved in study of testosterone production in fetal rat
- Mechanisms of scar formation in lung cells after exposure to nanoparticles
- SIRT1 regulates retinoic acid signaling and stem cell differentiation
- Histone-fold domain protein NF-Y promotes chromatin accessibility for cell specification
- Duking it out? My CA2 made me do it

NTP involved in study of testosterone production in fetal rat

NTP researchers contributed to a study that found *in utero* exposure to the cholesterol-lowering drug simvastatin lowers fetal testosterone production and fetal lipid profiles in both male and female rats. Exposure to simvastatin, combined with a plasticizer, dipentyl phthalate (DPeP), appeared to additively reduce testosterone production, despite distinct modes of action for the two chemicals. Reduced testosterone levels disrupt androgen signaling in the early fetus, which may contribute to congenital disorders.

The authors exposed time-mated rats for 5 days, during the critical developmental window of sexual differentiation, to simvastatin, DPeP, and a mixture of both, to assess dose-response effects on fetal testosterone production. In addition to finding that simvastatin exposure altered fetal lipid profiles, they observed that it reduced testosterone production by lowering cholesterol levels, a precursor in testosterone biosynthesis.

Exposure to DPeP is known to lower testosterone production through downregulation of the genes involved in steroid synthesis. The authors report that these different modes of action allow the mixture of simvastatin and DPeP to additively decrease testosterone production. The dose-response effect on gene expressions through gene array experiments further confirmed no overlap in the actions of simvastatin and DPeP.

This study highlights the potential reproductive and developmental defects in humans as a consequence of inadvertent exposure to statin drugs during early pregnancy. **(RG)**

Citation: Beverly BE, Lambright CS, Furr JR, Sampson H, Wilson VS, McIntyre BS, Foster PM, Travlos G, Gray LE Jr. 2014. Simvastatin and dipentyl phthalate lower ex vivo testicular testosterone production and exhibit additive effects on testicular testosterone and gene expression via distinct mechanistic pathways in the fetal rat. Toxicol Sci; doi:10.1093/toxsci/kfu149 [Online 23 July 2014].

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Mechanisms of scar formation in lung cells after exposure to nanoparticles

Scientists at the NIEHS Clinical Research Unit determined a new mechanism by which multiwalled carbon nanotubes induce scar formation in the lung. Because nanotube use is projected to increase in multiple applications, including electronics, composite materials, and engineering, this work will help researchers understand how these particles lead to airway scarring.

The team collected human bronchial epithelia, or cells that line the airways, from volunteers and exposed the cells to carbon nanotubes. The researchers discovered that the nanotubes caused a specific type of response, called NLRP3 inflammasome activation, and cell death. They then exposed lung fibroblast cells, which are responsible for scar formation after injury, to culture media that had previously bathed the injured lung cells. The fibroblasts were induced by these media to produce scar tissue, but did not do so when the investigators neutralized inflammasome-specific messaging molecules.

This work builds upon science that suggests airway-lining cells play an important role in the lung response to inhaled pollutants. It also lays the groundwork for further research that will focus on how preexisting airway disease, such as asthma, may further complicate the development of lung scarring after exposure to carbon nanotubes. **(JH)**

Citation: Hussain S, Sangtian S, Anderson SM, Snyder RJ, Marshburn JD, Rice AB, Bonner JC, Garantziotis S. 2014. Inflammasome activation in airway epithelial cells after multi-walled carbon nanotube exposure mediates a profibrotic response in lung fibroblasts. Part Fibre Toxicol 11:28.

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SIRT1 regulates retinoic acid signaling and stem cell differentiation

NIEHS researchers and their collaborators have shed light on the mechanisms by which the cellular metabolic sensor Sirtuin 1 (SIRT1) regulates stem cell differentiation and mouse embryonic development. SIRT1 is a protein deacetylase that coordinates the activation of transcription factors in response to cellular stress, which allows the cell to react to environmental cues. The study demonstrates that the stem cell differentiation signals stemming from retinoic acid (RA), an active metabolite of vitamin A, involve SIRT1.

In mice, deletion of SIRT1 results in embryonic lethality and severe developmental defects in surviving offspring. The authors show that loss of SIRT1 in mouse embryonic stem cells accelerates RA-induced differentiation. The authors were able to demonstrate that hyperacetylation of cellular retinoic acid binding protein II (CRABPII) at amino acid K102 is partially responsible for the RA-mediated hyperdifferentiation of SIRT1 deficient embryonic stem cells.

In addition, they found that whole body SIRT1-deficient mice exhibit elevated RA signaling at early stages of development. Furthermore, hepatic specific deletion of SIRT1 led to an increase in many RA target genes in response to exogenous RA in adult mice. Enhanced RA signaling likely underlies many of the developmental defects seen in the SIRT1 deficient mice. Understanding the signaling pathways that SIRT1 is responsible for mediating will provide insight into how the environment affects mammalian development. **(SW)**

Citation: Tang S, Huang G, Fan W, Chen Y, Ward JM, Xu X, Xu Q, Kang A, McBurney MW, Fargo DC, Hu G, Baumgart-Vogt E, Zhao Y, Li X. 2014. SIRT1-mediated deacetylation of CRABPII regulates cellular retinoic acid signaling and modulates embryonic stem cell differentiation. Mol Cell 55(6):843-855.

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Histone-fold domain protein NF-Y promotes chromatin accessibility for cell specification

Researchers from NIEHS have unearthed a novel function for NF-Y in promoting chromatin accessibility and specification of cell identity. Histone-fold protein NF-Y, a ubiquitously expressed transcription factor, was previously known for its role in the regulation of cell cycle progression in proliferating cells. These key findings were published in the journal Molecular Cell.

The authors investigated the function and mechanism of action for NF-Y using genome-wide occupancy and transcriptomic analyses in embryonic stem cells and neurons. They discovered that NF-Y uses distinct modes to regulate housekeeping and cell identity programs. Although NF-Y regulates housekeeping genes through cell type-invariant promoter-proximal binding, the authors also showed that NF-Y regulates genes required for cell identity by binding to cell type-specific enhancers. At these enhancers, NF-Y promotes the binding of master transcription factors by facilitating a permissive chromatin conformation. Based on these results, the authors propose a potential mechanism for NF-Y in the recruitment of pioneer transcription factors for cell specification. **(MM)**

Citation: Oldfield AJ, Yang P, Conway AE, Cinghu S, Freudenberg JM, Yellaboina S, Jothi R. 2014. Histone-fold domain protein NF-Y promotes chromatin accessibility for cell type-specific master transcription factors. Mol Cell 55(5):708-722.

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Duking it out? My CA2 made me do it

In collaboration with the National Institute of Mental Health (NIMH), researchers at NIEHS have discovered that activation of the vasopressin 1b receptor (Avpr1b) in a certain part of the brain is necessary for social aggression. Within the brain, this receptor is expressed uniquely in the CA2 region of the hippocampus, a part of the brain more commonly associated with learning and memory.

Earlier work from NIMH scientists showed that when the scientists knocked out the Avpr1b in mice, they saw a dramatic abatement of social aggression. When the authors replaced the lost receptor directly into CA2, aggressive behavior was restored to levels near that of normal mice. Social aggression is important for mothers protecting their young and for animals defending their territory. Interestingly, some neurons in the CA2 are missing in people who have schizophrenia.

To understand the mechanism of Avpr1b action, scientists measured the synaptic strength in brain slices from rats and mice. They found that vasopressin caused synaptic potentiation, but only in the CA2. Further studies indicated this response was exactly the same as that induced by oxytocin, which is another social neuropeptide. This research could lead to exciting new treatments for patients with psychiatric disorders who have inappropriate social aggression. **(SO)**

Citation: Pagani JH, Zhao M, Cui Z, Williams Avram SK, Caruana DA, Dudek SM, Young WS. 2014. Role of the vasopressin 1b receptor in rodent aggressive behavior and synaptic plasticity in hippocampal area CA2. Mol Psychiatry; doi:10.1038/mp.2014.47 [Online 27 May 2014]. [Story]

(Raj Gosavi, Ph.D., is a research fellow in the NIEHS Structure and Function Research Group. John House, Ph.D., is an Intramural Research Training Award (IRTA) fellow in the NIEHS Genetic Epidemiology Group. Mallikarjuna Metukuri, Ph.D., is a research fellow in the NIEHS Metabolism, Genes, and Environment Group. Simone Otto, Ph.D., is an IRTA fellow in the NIEHS Ion Channel Physiology Group. Shannon Whirledge, Ph.D., is a research fellow in the NIEHS Molecular Endocrinology Group.)

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Inside the Institute

NIEHS celebrates years of service with 2014 honorees

By Ian Thomas

Scientists and staff from across NIEHS gathered Sept. 8 in Rodbell Auditorium for the institute's annual Years of Service Awards ceremony. Hosted by NIEHS and National Toxicology Program Director Linda Birnbaum, Ph.D., the event recognized 64 institute employees, commemorating career milestones of 10, 20, 30, and 40 years, as well as 14 retirees.

"As federal employees, we work directly for the American people," said Birnbaum. "Here at NIEHS, that means maintaining a strong commitment to funding and supporting powerful research into the causes of disease. This requires a lot of hard work and dedication. But, beyond the hours, it also requires a very unique type of person to choose this as a career."

Assisted by NIEHS Deputy Director Richard Woychik, Ph.D., Birnbaum presented each honoree with a framed certificate celebrating his or her milestone, along with a congratulatory handshake of appreciation.

At the ceremony's conclusion, awardees were joined by colleagues, peers, and NIEHS leadership for a reception in the building 101 lobby.

Hunt, right, safety officer and deputy branch chief of the NIEHS Health and Safety Branch, accepts his award from Birnbaum. (Photo courtesy Steve McCaw)

Jones, right, is an administration specialist in the NIEHS Laboratory of Neurobiology. (Photo courtesy Steve McCaw)

Copeland, right, is lead researcher and chief of the NIEHS Laboratory of Molecular Genetics. (Photo courtesy Steve McCaw)

Lenox, right, is editor in chief of the Environmental Factor. (Photo courtesy Steve McCaw)

Employees and their milestones

10 years		
Helen Cunny	Paul Dunlap	Stephanie Hicks
Brigitte Horton	Hui Hu	Helena Kennedy
Angela King-Herbert	Kelly Lenox	Joe Lyerly
Leslie Lynch	Kindra Morrison	Nicholas Plummer
David Resnik	Andrew Rooney	Mark Rubino
Shepherd Schurman	Maria Sifre	Thomas Sliwa
Jennifer Smith	Kristina Thayer	Huanchen Wang
Myra Westmoreland	Vernee Wilson	Michael Wyde

20 years		
Warren Casey	Michele Cisco-Horton	William Copeland
Michael DeVito	Robin Mackar	Lee Ann McCray
RoseAnne McGee	Brian Moyer	Terrance O'Hanlon
Donna Sullivan	Vickie Walker	Kathryn Woods

30 years		
Donna Baird	Gordon Caviness	Bradley Collins
Glenda Corniffe	Rita Jones	Robert London
William Long	James Remington	Diane Spencer
Joan Sterling		

40 Years	
Deloris Anderson	June Dunnick
Thomas Hardee	Christopher Hunt

Retirees		
Beth Anderson	Lutz Birnbaumer	Dorothy Duke
Donald Ellis	Carolyn Flowers	Patricia Johnson
Larry Judd	Theodore Outwater	John Petranka
Richard Sloane	Sharon Soward	Christina Teng
Hugh Tilson	Michael Waalkes	

(Ian Thomas is a public affairs specialist with the NIEHS Office of Communications and Public Liaison, and a regular contributor to the Environmental Factor.)

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Future NIH administrative leaders visit NIEHS

By Kevin Selenich

A group of future National Institute of Health (NIH) science management, policy, and administrative leaders spent Aug. 28 on the NIEHS campus at Research Triangle Park, North Carolina, learning about NIEHS and its programs. Three NIH Management Interns and two Presidential Management Fellows traveled from Washington, D.C., to tour the institute, meet with scientific staff in both the internal research and grant programs, and to discuss potential rotations at NIEHS.

NIH has participated in the government-wide Presidential Management Fellows Program since 1985. Fellows develop rotational assignments across various NIH institutes and centers, in administrative and research support areas such as budget and finance, outreach and communications, information technology, grants management, program and management analyses, contracts management, human resources, and general administration. These opportunities provide on-the-job training with exposure to senior leadership.

The NIH Management Intern program was established in 1957 and has trained more than 400 staff members. The program offers the opportunity for highly motivated employees to explore different administrative fields, to gain invaluable insight into science management, and to change careers within NIH.

Experiencing life at NIEHS

Senior staff members highlighted a few of the Institute's unique programs:

- Sheila Newton, Ph.D. — overview of environmental health and NIEHS history
- Mary Wolfe, Ph.D. — National Toxicology Program (NTP)
- Kris Thayer, Ph.D. — NTP Office of Health Assessment and Translation
- Stavros Garantziotis, M.D. — Clinical Research Unit
- Chip Hughes — Division of Extramural Research and Training (DERT) Worker Education and Training Program
- William Suk, Ph.D. — DERT Superfund Research Program

In addition to hearing from the NIEHS scientific community, the group enjoyed lunch in the cafeteria with leaders from the Office of Management. Afterward, they had a tour of the Institute with John Schelp, Special Assistant for Community Engagement and Outreach, which was followed by a discussion with NIEHS Executive Officer Joellen Austin, touching on topics such as the opportunities and challenges of leading at NIEHS compared to other institutes and centers at NIH.

The visitors enjoyed a visit to the First Environments Early Learning Center, with a tour by office manager Kim Graber. They were impressed by the sustainable operations of the childcare center, including the edible gardens and the outdoor play space that was built with reclaimed materials.

At the close of the day, Mark McPherson, chief of staff for the U.S. Environmental Protection Agency Office of Administration and Resource Management, and Chris Long, deputy associate director for management, NIEHS Office of Management, discussed how the two organizations operate and collaborate on a shared campus.

The visitors also took part in a panel discussion with former fellows and interns, including Long, and, from DERT, Barbara Gittleman, Molly Puente, Jerry Phelps, and Jim Remington. Corey Liles, from the Research Triangle Foundation, provided a perspective on Research Triangle Park as a whole, presenting an overview of the past, present, and future of the Park.

Austin started her federal career as a Presidential Management Fellow and has sponsored the trip since her arrival at the institute in 2011. “I get as much out of this visit as do the interns and fellows,” she said. “I enjoy promoting the great work of NIEHS, and the enthusiasm of interns and fellows as they begin their management programs is contagious.”

(Kevin Selenich is a Presidential Management Fellow on assignment with the NIH Office of Management.)

Front row, from left, Amanda Garton, Ty Lawson, Austin. Back row, from left, Selenich, Amanda Roger, Richard Clinkscales, Andrew Nawrot. (Photo courtesy of Steve McCaw)

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NIEHS launches 2014 CFC drive

By Ian Thomas

NIEHS staff and scientists gathered Sept. 17 in Building 101 to kick off the institute's 2014 Combined Federal Campaign (CFC) drive. Working from tables in the lobby, volunteers served up a variety of tasty treats as part of a bake sale to advance the campaign's overall goal — raising $116,000 in charitable pledges by Dec. 1.

"Contributions to the CFC, even small ones, really make a profound difference in the lives of those they go to support," said Erik Tokar, Ph.D., a group leader with the National Toxicology Program (NTP).

Tokar is a co-chair on this year's campaign together with NTP Health Scientist Administrator Lori White, Ph.D.

Ashley Ascott, J.D., represents Dress for Success Worldwide, which is dedicated to improving the lives of women in 15 countries by providing professional clothing, employment retention programs, and career development support. (Photo courtesy of Steve McCaw)

A history of helping

Since 1961, the mission of the CFC has been to promote and support philanthropy through a program that is employee-focused, cost efficient, and effective in providing all federal employees the opportunity to improve the quality of life for people in need.

"The CFC has evolved into the largest employee giving program in the country," said NIEHS and NTP Director Linda Birnbaum, Ph.D. "I am so proud of the continued generosity of NIEHS employees. They are always willing to help those in need, especially when a charity addresses a need close to the heart that speaks to personal experiences."

This year, donors will notice one key difference — the ability to reach outside of their local community and give to any of the campaign's more than 24,000 charities nationwide.

"With this new option," noted Birnbaum, "any employee, anywhere, can log onto the campaign's website and find that one charity that speaks to him or her."

Employees can make a donation by cash, credit card, check, or by setting up a regular payroll deduction. Organizers stressed their preference for the latter, because it allows charities to better gauge their income for the year ahead.

Tokar encouraged NIEHS employees to take advantage of the payroll deduction feature. (Photo courtesy of Steve McCaw)

(Ian Thomas is a public relations specialist with the Office of Communication and Public Liaison and a regular contributor to the Environmental Factor.)

Birnbaum shared her pride in the 2013 success of the CFC, when NIEHS raised $100,425 for charity. (Photo courtesy of Steve McCaw)

White, center, listened as representatives of four CFC charities discussed their services with kickoff attendees. (Photo courtesy of Steve McCaw)

Upcoming 2014 CFC Events

Fun Run/Walk, Oct. 1 — A joint event hosted by EPA.

Charity Fair, Oct. 23 — To be held in conjunction with the NIEHS Fall Fest.

Halloween Lake Parade, Oct. 28 — A joint NIEHS and EPA fundraising event.

Bake Sale, Nov. 18 — Baked goods will be available in both 101 and Keystone.

Book Sale and Silent Auction, Nov. 18-20 — To be held in 101/C-Mall.

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National Institute of Environmental Health Sciences

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