**NIEHS Spotlight**

**Birnbaum joins community leaders at forum in Brooklyn**
A tour and forum featured Birnbaum in dialogue with community members and leaders regarding environmental health concerns in Brooklyn.

**NC State and UC Davis join NIEHS environmental health science research centers**
NC State and the University of California, Davis join the group of NIEHS-funded centers providing cutting-edge environmental health science expertise.

**Alternatives to PFASs: perspectives on the science**
Linda Birnbaum, Ph.D., and Philippe Grandjean, M.D., D.M.Sc., respond to the debate on use and replacement of the ubiquitous chemicals known as PFASs.

**NIEHS Biomedical Career Symposium inspires and informs hundreds**
More than 300 graduate students and postdocs sought inspiration and advice at the 18th annual career symposium, organized entirely by trainees.

**Xiaoling Li, Ph.D., receives tenure**
Li, who studies the molecular signaling pathways that govern aging, was awarded tenure by NIH on April 6.

**Clinical Feature**

**NIH renews asthma research commitment for World Asthma Day**
NIH is one of three institutes at the National Institutes of Health involved in asthma research and is recruiting patients for a clinical study.

**Science Notebook**

**Nano consortium concludes five years of scientific advances and collaboration**
The NIEHS research consortium on health effects of nanomaterials met May 6-7 to review findings they hope will influence nanoparticle design.

**NIEHS team solves ovarian cell mystery, shedding new light on reproductive disorders**
In a Nature Communications paper, Humphrey Yao, Ph.D., and colleagues revealed the origin of ovarian theca cells and shed light on cell communication.

**Distinguished Lecture highlights circadian rhythms**
John Hogenesch, Ph.D., discussed the far-reaching effects of circadian rhythms on physiology and behavior, and the implications for treatment of disease.
Birnbaum weighs in on flame retardants in RetroReport

The online news documentary Retro Report features Linda Birnbaum, Ph.D., discussing flame retardants and their health effects.

SRP researcher elected to National Academy of Sciences

Julian Schroeder, Ph.D., a scientist with the Superfund Research Program at the University of California, San Diego, was elected April 28 to the NAS.

NIH Poster Day encourages postbacs to pursue careers in research

Four NIEHS postbaccalaureate fellows participated in NIH Postbac Poster Day, and three won outstanding poster awards.

Grantees Hricko, Froines, and Gottlieb honored, set to retire

The East Yard Communities for Environmental Justice recognizes the contributions of Andrea Hricko and John Froines, Ph.D., in Los Angeles.

Tell about your work on climate change and children’s health

The President’s Task Force on Environmental Health Risks and Safety Risks to Children is collecting stories of actions to protect children from effects of climate change.

Gilbert sheds light on the microbiome and its invisible influence on health

Jack Gilbert, Ph.D., discussed the fascinating world of the human microbiome and its influence on health and disease in a May 7 Keystone lecture.

Andres awarded EMM New Investigator Best Paper

NIEHS visiting fellow Sara Andres, Ph.D., was honored for a paper that was also named the January 2015 issue Editor’s Choice.

Expert panel identifies research needs on high folic acid intake

NTP and the NIH Office of Dietary Supplements asked scientists to determine research needs related to health effects of high folic acid levels.

GEMS meeting showcases new genetic research funded by NIEHS

The Genetics and Environmental Mutagenesis Society April 27 meeting explored how genetic variation shapes host response, featuring NIEHS researchers and grantees.

NIEHS celebrates core support on Genomics Day

NIEHS scientists gathered May 7 to learn more about the network of core genomics support that the institute provides for its researchers.
Health and Fitness Week returns to NIEHS
May 4 marked the start of Health and Fitness Week at NIEHS, held annually to promote exercise, nutrition, and wellness among institute staff.

Extramural Research

Extramural papers of the month

- Reduced air pollution during Beijing Olympics linked with higher birth weights
- Early exposure to arsenic decreases lung function in children
- How alpha-synuclein causes Parkinson’s-associated neural damage
- BPA exposure shows transgenerational effects on reproductive health

Intramural Research

Intramural papers of the month

- NTP finds that arsenic induces multiple cancer characteristics in lung cell model
- Mammalian milk secretion uses novel mechanism
- The origins of the ovarian theca cells
- New biomarkers could screen endocrine-disrupting chemicals
- Long repetitive sequences drive some types of mutations

Calendar of Upcoming Events

- June 2-3, 8:30 a.m. – 5:00 p.m., in Rodbell Auditorium — National Advisory Environmental Health Sciences Council meeting, webcast
- June 4, 9:30 – 11:30 a.m., in D450 — Epigenetic and Stem Cell Biology Laboratory Seminar Series with John Rinn, Ph.D., of Harvard University
- June 4 (off-site event), 12:30 – 5:00 p.m., at the NIH Cloister Lecture Hall in Bethesda, Maryland — “Workshop on Reproducibility of Data Collection and Analysis — Modern Technologies in Genome Technology: Potentials and Pitfalls,” register
- June 8-9, June 8, 9:00 a.m. – 4:30 p.m.; June 9, 9:00 – 11:30 a.m., in Rodbell Auditorium — U.S. Department of Health and Human Services Climate Justice Conference
- June 11-12, June 11, 8:30 a.m. – 5:00 p.m.; June 12, 8:30 a.m. – noon, in Rodbell AB — “Workshop on New Approaches for Detecting Environmentally-induced DNA Damage and Mutation in Population Studies”
- June 16, 8:30 a.m. – 4:15 p.m., in Rodbell Auditorium — NTP Board of Scientific Counselors meeting, register to attend in person or via webcast
- June 25, 2:00 – 4:30 p.m., in Rodbell Auditorium — NTP Technical Report Peer Review meeting for pentabromodiphenyl ether mixture DE-71 (technical grade), register to attend in person or via webcast

View More Events: NIEHS Public Calendar

This month in EHP
This month’s Environmental Health Perspectives considers how temperature-related changes in air quality affect potential health impacts of climate change.
Birnbaum joins community leaders at forum in Brooklyn

By Eddy Ball

NIEHS and National Toxicology Program Director Linda Birnbaum, Ph.D., spoke at the latest community forum May 21 in Brooklyn, New York. The forum series, which began in 1998, has featured directors of NIEHS at grassroots meetings in communities across the nation.

The evening forum and an afternoon bus and walking tour of Brooklyn’s Sunset Park community (see text box) were hosted by UPROSE, Brooklyn’s oldest community-based Latino organization dedicated to environmental justice. UPROSE Executive Director Elizabeth Yeampierre, J.D., is a former member of the NIEHS National Advisory Environmental Health Sciences Council.

The forum featured Birnbaum and community leaders in dialogue with members of the community, in what was billed as a post-Hurricane Sandy “Community Conversation on Toxic Risk, Climate Change, and Health.”

“We look forward to continuing our support for environmental health and justice research, and working with community members, local officials, scientists, health care providers, and other partners here,” Birnbaum said in her opening remarks.

Hearing from the community

Joining Birnbaum and people from Sunset Park were experts and community leaders, including Yeampierre; Eddie Bautista, executive director of the New York City Environmental Justice Alliance; New York City Council member Carlos Menchaca; and 12-term 7th Congressional District Representative Nydia Velazquez (D-NY).

In her remarks, Birnbaum proudly described the NIEHS commitment to environmental health research, which totaled $25 million dollars in New York City for fiscal year 2014.
During that same period, the institute devoted $62 million to climate-related exposures and conditions, which were underscored for New Yorkers by the massive flooding caused by Hurricane Sandy in 2012. In response to that disaster, UPROSE launched the Sunset Park Climate Justice and Community Resiliency Center, New York City’s first grassroots-led, bottom-up, climate adaptation and community resiliency planning project.

“My institute spent more than $265 million [in FY2014] studying toxic chemicals, toxic exposures, toxic substances, pesticide toxicity, and neurotoxicants,” Birnbaum added. All of these are major concerns for the people of Sunset Park.

For the panelists, the forum was an opportunity to hear the public’s environmental concerns and to share their own efforts to address those concerns. For the community, it was an opportunity to get the attention of people who could provide resources and shape policy.

Thanks to careful planning by Yeampierre and the UPROSE staff, the tour and forum were well-organized and engaging. As Melissa del Valle Ortiz, board president of the League of Women Voters of New York City, said, “We are lucky and blessed to have a community-based organization like UPROSE that knows what it takes to get things done.”

The “Welcome to Brooklyn” message was juxtaposed with the entrance to one of the city’s busiest interstate highways, which crosses the length of Sunset Park. (Photo courtesy of John Schelp)
Brownfields, such as this one framing a view of the new World Trade Center building across the Hudson River, are the result of generations of unregulated waste and hazardous chemical disposal. (Photo courtesy of John Schelp)

Yeampierre described sources of pollution as the visitors rode past factories in a bus provided by NHM, which is known for bringing science to the community, including stuffed animals and skeletons. (Photo courtesy of John Schelp)

At the evening forum, Birnbaum and Yeampierre heard from Menchaca, center, who represents a diverse district in New York, including a large Chinese and Latino immigrant population, the second largest public housing development in the city, and a waterfront community heavily affected by Hurricane Sandy. (Photo courtesy of John Schelp)

Birnbaum and Bautista, center, reacted to comments from Velazquez. (Photo courtesy of John Schelp)

Community members participated in the forum to hear and be heard by their representatives and advocates. (Photo courtesy of John Schelp)
NC State and UC Davis join NIEHS environmental health science research centers

By Kelly Lenox

New research centers at North Carolina State University (NC State) and the University of California, Davis (UC Davis) join more than 20 NIEHS-funded Environmental Health Sciences (EHS) Core Centers around the country working at the cutting edge of environmental health research, and fostering community engagement. NIEHS issued the five-year awards April 29 and May 5, respectively.

“Our EHS Core Centers program is a network of leaders in environmental health sciences,” said Claudia Thompson, Ph.D., head of the NIEHS Population Health Branch and program lead. “They bring together scientists from multiple disciplines to pursue promising research opportunities, and to develop the next generation of EHS researchers. We are very excited to have NC State and UC Davis join the network.”

North Carolina collaboration

At NC State, scientists at the Center for Human Health and the Environment (CHHE) will collaborate with researchers at the East Carolina University Brody School of Medicine, North Carolina Central University, North Carolina Department of Health and Human Services, and Research Triangle Institute NIH Eastern Regional Comprehensive Metabolomics Resource Core. Leveraging the technical expertise of CHHE and its partners, the center will focus on how environmental stressors interact with biomolecular signaling pathways, the genome, and the epigenome.

“CHHE will build on NC State’s unique research and community outreach strengths to make significant contributions to understand and prevent adverse impacts of environmental factors on human health,” said Robert Smart, Ph.D., NC State cancer researcher and CHHE director.

Multidisciplinary team and California community partnerships

The new center at UC Davis comprises a team of scientists from 19 departments, across four schools and colleges. “The NIEHS core center award is an exciting development that will enable our multidisciplinary team of environmental health scientists at UC Davis to expand our scope of research on risks to respiratory, brain, immune, endocrine, and metabolic functions,” said Irva Hertz-Picciotto, Ph.D., director of the center.

In addition to leading CHHE, Smart serves as director of graduate programs for the NC State Department of Environmental and Molecular Toxicology and heads the NIEHS training program Molecular Pathways to Pathogenesis in Toxicology. (Photo courtesy of Jonathan Hall)

Hertz-Picciotto, a well-known environmental epidemiologist, was one of the panelists in the NIEHS virtual community forum on autism in April 2014 (see story). (Photo courtesy of Steve McCaw)
Exposures of interest include particles and volatile organic compounds in ambient air, pollutants in drinking water and food, and household or personal care products. Hertz-Picciotto expressed excitement about the upcoming work the center will do, especially in California’s Central Valley. “Most significantly, this new center will address serious health disparities and seek environmental justice with respect to chemical pollutants that abound in the California Central Valley,” she said, “by partnering with communities in the San Joaquin Valley and translating scientific research findings into public health measures that reduce pollutant levels and improve the health and quality of life for all residents.”

Return to Table of Contents

Alternatives to PFASs: perspectives on the science

The NIEHS journal Environmental Health Perspectives (EHP) published an editorial May 5 by Linda Birnbaum, Ph.D., director of NIEHS and the National Toxicology Program, and Philippe Grandjean, M.D., D.M.Sc., of the Harvard School of Public Health and the University of Southern Denmark. The editorial addressed two briefs published the same day in EHP. The first, known as the Madrid Statement, called for cooperation in limiting the production and use of a class of compounds known as polyfluoroalkyl and perfluoroalkyl substances, or PFASs. The second is a counterpoint to the Madrid Statement, from the FluoroCouncil.

The following is an excerpt from the Birnbaum and Grandjean editorial.

“Poly- and perfluoroalkyl acids (PFASs) are ubiquitous in our lives. These chemicals are used as surfactants and as water and oil repellents in a variety of consumer products such as cosmetics, food packaging, furnishings, and clothing. Since their initial marketing more than 60 years ago, extensive research has demonstrated that the long-chain PFASs are highly persistent, bioaccumulative, and toxic (Buck et al. 2011). As a result, they are being phased out in many countries. However, controversy has emerged regarding the safety of the most common alternatives, the short-chain PFASs.

“The [Madrid] statement defines a roadmap for scientists, governments, product manufacturers, purchasing organizations, and consumers to work together to limit the production and use of PFASs globally and to develop safer alternatives.

“In a response to the Madrid Statement in this issue of EHP, the FluoroCouncil, which represents the world’s leading fluorotechnology companies, agrees that it ‘could support many of these policy recommendations if they were limited to long-chain PFASs’ (Bowman 2015). The FluoroCouncil supports the call to action from the scientific and professional community to limit the production and environmental release of long-chain PFASs but states that ‘the short-chain PFAS substances studied to date are not expected to harm human health or the environment,’ as they ‘are eliminated more rapidly from the body and are less toxic than long-chain substances’ (Bowman 2015).
“Although there is agreement regarding the shorter human half-lives of short-chain PFASs, … recent publications … expressed concerns that fluorinated replacements are similar to the PFASs they replaced in terms of their chemical structure, environmental persistence, and hazardous potential for both the environment and humans. Given the fact that research raised concern about the long-chain PFASs for many years before action was taken and that global contamination and toxicity have been documented in the general population (Grandjean and Clapp 2014), potential risks of the short-chain PFASs should be taken into account when choosing replacements for the longer-chain compounds.

“It has been difficult to find substitutes that match the function and performance level of PFASs. … Significant innovation is thus required to find functional nonfluorinated alternatives to PFASs. The U.S. Environmental Protection Agency recently recognized such innovation by awarding its 2014 Designing Greener Chemicals Award to a halogen-free firefighting foam.

“Research is needed to understand the potential for adverse health effects from exposure to the short-chain PFASs, especially regarding low-dose endocrine disruption and immunotoxicity. In parallel, research is needed to find safe alternatives for all current uses of PFASs. The question is, should these chemicals continue to be used in consumer products in the meantime, given their persistence in the environment? And, in the absence of indisputably safe alternatives, are consumers willing to give up certain product functionalities, such as stain resistance, to protect themselves against potential health risks? These conundrums cannot be resolved by science alone but need to be considered in an open discussion informed by the scientific evidence.

Citations:


Birnbaum, who took the helm at NIEHS in January 2009, is the first woman and first toxicologist to lead the institute. (Photo courtesy of Steve McCaw)
The 18th annual NIEHS Biomedical Career Symposium opened April 25 with a warm welcome from NIEHS Director Linda Birnbaum, Ph.D., and a keynote address by Melanie Sinche of Harvard Law School. Sinche spoke to an estimated 300 attendees, mostly graduate students and postdoctoral researchers, who came to the U.S. Environmental Protection Agency (EPA) in Research Triangle Park, North Carolina for career guidance, skill development, and networking opportunities.

Birnbaum noted the importance of postdoctoral researchers and the variety of possibilities they can seek in their careers. “NIEHS has a responsibility to provide you opportunities for experience, for mentorship, and for support as you all transition to independent careers,” Birnbaum said.

Samantha Hoopes, Ph.D., co-chair of the Career Symposium Planning Committee, introduced several new features at the 18th annual event, including color-coded stickers to facilitate networking with others who share a career interest, and longer curriculum vitae (CV) and resume consultation appointments.

Hoopes and co-chair Kiersten Verhein, Ph.D., stepped forward to oversee the event shortly after the 17th annual Career Symposium and began work with the planning committee in the fall of 2014.

Learning how your skills transfer

Sinche’s talk, “But I Have No Skills! Debunking Myths and Exploring Career Options for Ph.D.s,” was informed by her work a senior research associate in the Labor and Worklife Program at Harvard Law School. She is the lead investigator on a survey study to identify career outcomes of students who earned Ph.D. degrees between 2004 and 2014. The survey is now closed, and Sinche is conducting an analysis of more than 8,100 responses.

Sinche kept the audience involved throughout her talk, beginning with survey responses by more than 200 of the registered attendees regarding their career paths of interest and what they hoped to learn at the event. The breadth of those responses impressed Sinche. “As recently as five years ago, the trainees that I worked with weren’t as aware of the vast array of possibilities,” she said.
Sinche debunked several myths, including “I’m only trained for one job,” which she said was based on the historical apprenticeship model of graduate study that no longer applies to today’s workforce. By sharing a sample job description and CV, she helped participants identify transferable skills and understand how an academic-oriented CV may not reflect those skills. Fortunately for participants, one-on-one CV consultations were available with more than 25 experts from a variety of job sectors.

“The content of your studies is critical, but that is not all you have to offer,” Sinche said. “The reality is that graduate students and postdocs possess a wide range of skills that are valued by employers across all sectors.”

Options and career planning

Concurrent sessions allowed participants to choose events most applicable to their interests, including eight expert panels from various career paths, 10 career development workshops, and a networking reception that featured exhibitors from local groups and companies.

Workshops focused on preparation for and identification of pathways to careers, including “Leveraging LinkedIn for Expertise Development and Career Opportunities” and “Managing Your Career with an Individual Development Plan.” Others highlighted self-assessment and development, with topics such as “Untrain Your Brain: Synergy Between Personal and Professional Interests” and “Leadership and You: Balancing Strength and Challenges.”
An opportunity close to home — planning the symposium

The planning of the symposium reflected one of Sinche’s central messages — take advantage of local opportunities to volunteer in ways that will develop transferable skills appreciated in every job sector. The event was organized and executed entirely by trainees at NIEHS and EPA (see sidebar), with support from the NIEHS Office of Fellows’ Career Development.

Trainees through the years have used the symposium to strengthen many of the transferable skills Sinche mentioned, such as problem solving, creativity, managing resources, and communicating effectively. The committee members personally invite panelists and workshop speakers, offering an extraordinary opportunity to network.

Sinche asked the graduate and postdoctoral researchers in attendance to assess their own skills, by reflecting on their most rewarding and positive experiences. (Photo courtesy of Steve McCaw)

In the writing and communication career panel, Robin Arnette, Ph.D., NIEHS science editor, encouraged listeners to get involved in science writing at their current institutions, to help propel their career. She and other panelists shared insights into their career paths and gave guidance in response to audience questions. (Photo courtesy of Steve McCaw)

Hoopes participates in a discussion session during a workshop by Patrick Brandt, Ph.D., director of Science, Training, and Diversity at the University of North Carolina at Chapel Hill (UNC), titled “How to Develop the Skills Needed for Careers in Science Outreach and Program Administration.” (Photo courtesy of Steve McCaw)

Diane Klotz, Ph.D., of Sanford-Burnham MRI, discussed assessing personal leadership style using specific leadership models, in her workshop, “Leadership and You: Balancing Strengths and Challenges.” (Photo courtesy of Steve McCaw)
Xiaoling Li, Ph.D., receives tenure

By Robin Arnette

When Xiaoling Li, Ph.D., joined NIEHS in 2007 as a tenure-track researcher, she knew that with a lot of hard work, this day would eventually come. On April 6, the National Institutes of Health Central Tenure Committee granted Li tenure, or a permanent research position. Li heads the NIEHS Metabolism, Genes, and Environment Group and focuses on the molecular signaling pathways that govern aging.

As a youngster, Li liked mathematics, but when she started high school, she became interested in biology. The simple DNA experiments she performed in class exposed her to endless research possibilities as a scientist. When she went to college, she chose biochemistry as her major and never looked back.

She earned a B.S. in biochemistry from Peking University, Beijing, an M.S. in molecular biology from the Chinese Academy of Sciences, Beijing, and a Ph.D. in biological chemistry from Johns Hopkins University School of Medicine, Baltimore. For her postdoctoral training, Li worked with Leonard Guarente, Ph.D., a Novartis Professor of Biology at the Massachusetts Institute of Technology, Cambridge, Massachusetts.

Sirtuins in Aging and Age-associated Diseases

As a leader in the field, Li sponsored a sirtuin symposium in 2011 that brought like-minded researchers to NIEHS.

The gathering resulted in several new collaborations. (Story)
Li said tenure provides the job security that allows her to focus more on research. “It permits me to test novel ideas that may be high risk, but have the potential for high gain,” she said.

Her work at NIEHS extends past her own research, to help train the next generation of scientists. Besides teaching the trainees in her lab, Li has also mentored students in the NIEHS Scholars Connect Program (see story).

**Examining the molecular mechanisms of aging**

Li and her group examine how human genes interact with the environment and how this action regulates human physiology. In particular, Li is interested in a family of proteins called sirtuins, which detect metabolic fluctuations in the body, as well as environmental changes that affect metabolism. Sirtuins can regulate transcription, metabolism, and the stress response, and have been implicated in human disease and aging.

SIRT1 is the most studied sirtuin, and scientists have witnessed its involvement in a diverse range of organisms, such as yeast, roundworms, flies, and mice.

“We study the function of SIRT1 in age-associated illnesses, particularly metabolic diseases,” Li said. “By watching the activity of SIRT1 in mice, we can follow animals from youth to old age.”

**Birnbaum weighs in on flame retardants in RetroReport**

RetroReport, a New York Times online news documentary, examined the history of flame retardant use in consumer products in a May 3 video. The documentary, “Safety on Fire” includes concerns by Linda Birnbaum, Ph.D., director of NIEHS and the National Toxicology Program, about the health effects of flame retardants, especially in children.

The RetroReport series selects news stories from the past and looks forward to see how the matter evolved in the years that followed.

Birnbaum is featured on the video at the following times — 6:17; 11:49; and 12:52.

*Return to Table of Contents*
SRP researcher elected to National Academy of Sciences

By Anne Frances Johnson

Plant biologist Julian Schroeder, Ph.D., was awarded one of the highest honors in science April 28 — membership in the prestigious National Academy of Sciences (NAS). Schroeder’s work in the University of California, San Diego (UCSD) Superfund Research Program (SRP) sheds light on how plants may help clean up soil and water that is contaminated with heavy metals.

“Julian has been a part of the SRP for more than 15 years,” said William Suk, Ph.D., director of the NIEHS Superfund Research Program and chief of the Hazardous Substances Research Branch. “He is an outstanding scientist whose basic research is being translated in a number of ways to improve human health. Plus, he is a really nice guy,” Suk continued. “His election to the NAS is certainly well-deserved.”

Pioneering plant discoveries may solve difficult problems

Schroeder is widely recognized for his early groundbreaking work on plant ion channels, the molecular valves in cellular membranes that control the movement of ions into and out of the cell. Currently, Schroeder’s lab is investigating the genes encoding plant ion channels, particularly those that play a role in the ability to tolerate stresses, such as drought, salinity, and heavy metals.

Studying how some plants are able to thrive in challenging, even highly toxic, environments may shed light on new ways to contain or clean up hazardous substances. Schroeder’s work with the NIEHS-funded UCSD SRP focuses on the potential use of genetically engineered plant models for removal of heavy metals from soil and water. Two SRP Research Briefs have highlighted the team’s work on metal accumulation in plants and plants with natural resistance to heavy metals.

Illustrious honor for a distinguished career

Schroeder’s innovative work has earned him worldwide recognition and a number of awards and appointments. Novartis Chair and distinguished professor in the Division of Biological Sciences at UCSD, Schroeder directs the Plant Systems Biology Graduate Training Program and co-directs Food and Fuel for the 21st Century. He is also the current president of the American Society of Plant Biologists (ASPB), a professional society of over 4,000 members devoted to the advancement of the plant sciences.

Election to the National Academy of Sciences is one of the highest honors bestowed on U.S. scientists and engineers. NAS is a private, nonprofit organization established by Congress in 1863 to serve as an adviser to the federal government on matters of science and technology. The organization and its members provide unbiased advice to the nation and are dedicated to advancing science and its use for the general welfare.
NIH Poster Day encourages postbacs to pursue careers in research

By Geoffrey Feld

NIEHS sent four postbaccalaureate (postbac) Intramural Research Training Award (IRTA) fellows to the National Institutes of Health (NIH) Postbac Poster Day April 30 at the NIH campus in Bethesda, Maryland.

Three of the NIEHS fellows — Rebecca Evans, Collin Johnson, and Preeti Kodavanti — won outstanding poster awards at the event, and Lauren Donoghue, Evans and Kodavanti received travel awards from the NIH Office of Intramural Training and Education. All four expressed excitement about incorporating research into their career paths.

“I learned at the poster session that I really do enjoy talking about my work with other people and helping get them to a point of understanding,” Evans said. (Photo courtesy of Lauren Donoghue)

NIEHS presenters at NIH Postbac Poster Day

Lauren Donoghue (The University of North Carolina at Chapel Hill) — “A rodent-specific estrogen receptor beta isoform has tissue-specific expression and reduced transactivation with endocrine disrupting compounds”
Preceptor: Kenneth Korach, Ph.D.

Rebecca Evans (Davidson College) — “Basal regulation of the blood-brain barrier: turning down P-glycoprotein via PI3K/Akt/mTOR signaling”
Preceptor: David Miller, Ph.D.

Collin Johnson (The University of Texas at Austin) — “TLR5 modulates MyD88-dependent TLR4 signaling”
Preceptor: Stavros Garantziotis, M.D.

Preeti Kodavanti (The University of North Carolina at Chapel Hill) — “Mitochondrial protection accounts for decreased toxicity of nanoceria in macrophages compared to monocytes”
Preceptor: Stavros Garantziotis, M.D.
Gaining experience and recognition

NIH hosts over 600 postbacs at its institutes and centers (ICs) to expose recent graduates to careers in research. A major annual event, Postbac Poster Day offers fellows an opportunity to present their research, learn about science conducted at NIH, and network with colleagues for career development. While the vast majority of participants work on or near the main Bethesda campus, both NIH and the postbac mentors, known as preceptors, encourage postbacs at all ICs to participate.

Stravros Garantziotis, M.D., head of the NIEHS Matrix Biology Group and medical director of the NIEHS Clinical Research Unit, has hosted eight postbacs since he joined the institute in 2008. “I find it rewarding to mentor [postbacs] in this stage of their careers and go through the process with them,” he said.

This year he encouraged his two postbacs, Johnson and Kodavanti, to attend Poster Day. Both of them, together with Evans, scored in the top 20 percent of all presentations, earning them outstanding poster awards. A panel of graduate students, postdoctoral and clinical fellows, staff scientists, and clinicians served as judges for the event.

“The NIH postbac program is one of few opportunities for recent graduates to tackle full scientific projects and receive training,” said Donoghue. That may explain why undergraduate research advisors, including those of Donoghue, Evans, and Johnson, are so quick to recommend the program to motivated students. And, why graduate schools are “very pleased to see this training on my application,” Donoghue added.

Presenting for the future

All four NIEHS postbacs reported that Poster Day was a valuable experience that helped solidify their interests in research. From networking with potential collaborators to communicating their science, the fellows felt they made the most of their travel.

 “[The event] sparked my interest in pursuing clinical research during my medical career,” said Kodavanti, who starts medical school at Georgetown University this fall. Johnson added, “[Participating] helped direct my interests and intended career objectives towards exploring joint pulmonary-cardiovascular problems.”

Given that fellows at NIEHS are geographically separated from a variety of training resources, their strong showing is all the more remarkable. Recognizing this dilemma, Donoghue said that attending Poster Day was her way of taking advantage of these resources. “Many postbacs we met were not aware of NIEHS,” she noted, explaining that she felt the event provided an important opportunity for NIEHS postbacs to “be more active in their community and spread the word about the institute’s research mission.”

(Geoffrey Feld, Ph.D., is an Intramural Research Training Award fellow in the NIEHS Genome Stability Structural Biology Group.)

Return to Table of Contents
Grantees Hricko, Froines, and Gottlieb honored, set to retire

By Eddy Ball

The East Yard Communities for Environmental Justice (EYCEJ) will recognize NIEHS grantees Andrea Hricko, John Froines, Ph.D., and Robert Gottlieb for their commitment to environmental justice and community engagement at a June 6 dinner and celebration in Los Angeles. All three are transitioning into retirement from academic careers.

Hricko is a professor of clinical preventive medicine at the University of Southern California (USC) Keck School of Medicine and the long-time director of the Community Outreach and Engagement Core of the NIEHS-funded Southern California Environmental Health Sciences Center, which is directed by Frank Gilliland, M.D., Ph.D.

“Being honored by a community group that is our partner in translating research to policy and prevention is especially gratifying,” Hricko said.

Trained as a physical-organic chemist, Froines is a professor emeritus at the University of California, Los Angeles Fielding School of Public Health. He also serves as associate director and head of the Exposure Assessment Research Core at the Southern California Environmental Health Sciences Center.

Gottlieb, who is a distinguished professor at Occidental College, is also a well-known author and advocate for environmental health. He led an NIEHS-funded environmental justice project 2003-2009 focused on access to healthy food options in Los Angeles neighborhoods.

The paths of these scholar-activists have crossed many times, including at the 2012 Heroes for Health Gala Dinner in Los Angeles, where Gottlieb presented awards to Hricko and Froines for lifetime achievement in environmental health, from Physicians for Social Responsibility-Los Angeles (PSR).

Collaborating for community environmental health

Hricko, Froines, and Gottlieb have worked together with EYCEJ and other community groups on a variety of environmental justice issues since 2000, most notably the Trade, Health & Environment Impact Project. This community-academic partnership led to the formation of a nationwide network of groups working to reduce pollution in communities affected by the movement of goods into and out of ports and transfer facilities.
“Andrea has been at the forefront of community engagement and research translations for meaningful environmental public health impacts,” said Liam O’Fallon, coordinator of the NIEHS Partnerships for Environmental Public Health program. “It has been amazing to see the outcomes of her collaborative work on the goods movement. She has trained students, empowered community groups, and raised the awareness of her academic and governmental partners. I am going to miss working with her.”

Froines, center, was honored in 2013 by election to the Collegium Ramazzini (see story). Joining him were Hricko, right, to whom he has been married since early in their careers, and fellow NIEHS grantee Philip Landrigan, M.D. (Photo courtesy of Omar Gavioli)

Career paths with twists and turns

The honorees all have interesting histories, but Hricko may have the most varied experience, which uniquely prepared her for her award-winning work in community engagement. Hricko will have directed the community outreach and engagement program at the NIEHS-funded center for more than 15 years, when she transitions from partial to full retirement in 2016.

Prior to joining the USC center in 2000, Hricko had worked for a public interest group; for the University of California, Berkeley in a worker safety program; as a news producer of health, environment, and investigative stories for KCBS-TV; and as deputy assistant secretary of labor for the Mine Safety and Health Administration in the Clinton administration. Along the way, she also produced several documentary films.

Hricko also brought her expertise to NIEHS, giving talks about her community-engaged research on health impacts of air pollution from port, rail, and road transportation in the Los Angeles area (see story), and serving a term on the NIEHS National Advisory Environmental Health Sciences Council from 2010 to 2014.

Hricko has published a number of studies and commentaries, including her most recent one — a 2012 news article in the NIEHS journal Environmental Health Perspectives, Progress and pollution: port cities prepare for the panama canal expansion.

Froines is known for both his contributions to environmental public health and his role in the 1960s anti-war and civil rights movements. He has received a number of honors for his groundbreaking research on air pollution and hazardous chemicals, his advocacy of public health and worker safety, and his public service at state, local, and national levels.

Gottlieb is the author and co-author of numerous books and other publications, including “Food Justice”; “Reinventing Los Angeles: Nature and Community in the Global City”; and “The Next Los Angeles: The Struggle for a Livable City.” A longtime environmental and social justice activist, Gottlieb has researched and participated in social movements for more than 50 years.
Bringing it to the streets — putting science to work in communities

Through grass-roots organizing and building leadership skills, EYCEJ helps underrepresented communities get involved with policy makers and other agencies to promote environmental justice policies that protect the health of local, regional, and statewide residents.

As the organization said in its announcement, “After more than a decade of service as EYCEJ academic allies, we would like to celebrate the legacies of Andrea Hricko, John Froines, and Robert Gottlieb as they transition out of their academic institutional careers and into new projects.”

(Eddy Ball, Ph.D., is a contract writer for the NIEHS Office of Communications and Public Liaison.)

Tell about your work on climate change and children’s health

By Kelly Lenox

The President’s Task Force on Environmental Health Risks and Safety Risks to Children is seeking stories on policy actions and programs to protect children from the effects of climate change. The project is being called the policy roundup. NIEHS co-chairs the task force’s Subcommittee on Climate Change, along with the U.S. Environmental Protection Agency and the Department of Homeland Security.

“We know that children are among the most vulnerable to climate change’s health effects, due to their developing bodies, dependence on others, and unique exposure scenarios,” said NIEHS program analyst Kimberly Thigpen Tart, J.D., who serves as co-chair of the subcommittee. “The goal of the policy roundup is to highlight effective ways people are taking action to protect children’s health.”

The task force is gathering examples of policy actions and programs at the federal, state, local, and tribal levels, aimed at protecting children’s health against the impacts of climate change. Any member of the public is welcome to submit a story, many of which will be highlighted on the task force website and at a special event during Children’s Health Month in October. The stories will also be disseminated to raise awareness, share what is working, and encourage others to adopt similar policies.

Stories should describe the policy action, who initiated it and why, the goal, any evaluation metrics, the initiator’s website address, and any other information that would be helpful to the community. The length should not exceed 500 words.

Submissions may be made online at Climate Change and Children’s Health Policy Roundup and may include up to three photos, videos, or related materials, such as handouts, training tools, or apps. The deadline for submission is July 10.
NIH renews asthma research commitment for World Asthma Day

On World Asthma Day 2015, the National Institutes of Health (NIH) stood with the international community to renew their commitment to advance the understanding of asthma and develop effective strategies to manage and prevent the disease. Within a broad asthma research portfolio, NIH-supported scientists are making progress in understanding how certain exposures, such as microbes, allergens, and pollution, may contribute to the development or worsening of asthma, and they are working on new approaches to address these factors.

An estimated 300 million people worldwide are living with asthma, which is a chronic disease that inflames and narrows the airways of the lungs, causing wheezing, breathlessness, chest tightness, and coughing. Globally, an estimated 15 million years of life are lost each year due to asthma-related disability or early death. Asthma is a leading cause of hospitalization and missed school and workdays in the United States, and managing the condition can be costly for families and health care systems.

The National Institute of Allergy and Infectious Diseases; the National Heart, Lung, and Blood Institute; and NIEHS are the lead NIH institutes that support and conduct asthma research. Among many other asthma-related projects, scientists supported by these institutes are working to advance knowledge of how exposures affect asthma development and severity. These studies underpin NIH efforts to reduce the worldwide burden of asthma and improve the quality of life for people with this chronic disease.

Research at NIEHS

NIEHS research focuses on how the environment contributes to diseases such as asthma. Research has shown that environmental exposures, such as parental smoking, can play an important role in the initiation and severity of asthma, particularly in children. Recent work at NIEHS suggests that maternal smoking during pregnancy may have transgenerational effects on asthma development.

Studying indoor and outdoor exposures, as well as genetics, helps researchers develop cost-effective interventions and novel treatments for asthma. In 2015, the NIEHS Clinical Research Unit began recruiting patients for the Natural History of Asthma with Longitudinal Environmental Sampling study (NHALES).

NHALES will help scientists understand how the environment affects asthma symptoms. In particular, NIEHS scientists will examine how bacteria living in and on humans and in their homes, known collectively as the microbiome, may be associated with asthma activity. This five-year study will provide free treatment, medications, and compensation so participants can get their asthma under control (see story).

(Based on the NIH press release for World Asthma Day)
Nano consortium concludes five years of scientific advances and collaboration

By Kelly Lenox

In 2010, NIEHS established a consortium of research centers to study the health effects of engineered nanomaterials for five years. As the project came to a close, consortium researchers gathered for a final meeting May 6-7 at Research Triangle Institute (RTI) International in Research Triangle Park, North Carolina, to share their scientific advances and discuss the challenges ahead.

Sri Nadadur, Ph.D., program director for the NIEHS Nanotechnology Environmental Health and Safety program, described the consortium’s threefold research agenda. “We wanted researchers to address cellular and molecular level activity, then transfer those findings to animal studies,” Nadadur explained. “And we wanted to take those observations and develop predictive modeling for risk assessment.”

With more than 20 grantees, including eight research centers and several individual researchers, the consortium structure provided a means to share results and discuss challenges, Nadadur said. As a way to focus research, all grantees studied silver nanoparticles and multiwalled carbon nanotubes provided by NIEHS. In addition, researchers chose various other nanomaterials to study, including metal oxides, silica oxide, silver nanowires, carbon 60, and quantum dots.

Strategic, groundbreaking research

NIEHS and National Toxicology Program Director Linda Birnbaum, Ph.D., welcomed researchers. “The nano environmental health research program has become an important component in three strategic goals of the NIEHS strategic plan,” she said.

Engineered nanomaterials (ENMs) are synthetic particles with any external dimension between 1 and 100 nanometers. They are at the forefront of a number of advances in medicine, technology, and consumer products, and until recently, little was known about their health effects.

According to Nadadur, groundbreaking consortium research has been featured at diverse national and international scientific meetings, including the Society of Toxicology and the American Chemical Society. (Photo courtesy of Steve McCaw)

Hernan Navarro, Ph.D., above, and Tim Fennell, Ph.D., not shown, are both with RTI International, which hosted the event. “NIEHS is grateful for the work they put in to make this meeting a success,” Nadadur said.
Two days of research presentations, posters, and discussions revealed that consortium researchers have made significant inroads toward understanding the mechanisms of physiological responses to nanoparticle exposures, from rates of cellular uptake to inflammatory and cytotoxic responses.

Researchers also explored how those responses could be moderated by the size, charge, coating, and surface chemistry of the particles. “Two centers clearly demonstrated, at the cellular and animal levels, how physical and chemical properties influence cellular response,” said Nadadur, who reviewed the highlights of the consortium results (see sidebar). “The consortium achievements in addressing the goals of nano environmental health are greater than any one individual effort,” he added.

**Insights to guide future designs**

According to Nadadur, one of the NIEHS goals for the consortium was to make advances that would help guide the design of the next generation of nanomaterials. That goal was met, as evidenced by findings shared by several presenters.

For example, the team at the University of California, Los Angeles Center for Nanobiology and Predictive Toxicology explored whether there were unique nanoscale characteristics that contributed to hazards in the lung. Andre Nel, Ph.D, described their discovery that the effects of zinc oxide were less toxic when some of the zinc oxide particle’s surface was coated with iron in a controlled manner.

The center at the University of California, Davis also studied respiratory effects. Kent Pinkerton, Ph.D., discussed his team’s findings on how the surface coating of nanoparticles influenced the effects of exposure. “If we can work toward modifying the ways in which nanomaterials are synthesized, while maintaining their marvelous properties, I think we can find ways to create materials that are less toxic,” he said.

**Results lead to next steps**

By the end of 2014, more than 200 papers on consortium research had been published, and scores more are in review or preparation stages. NIEHS is using the results of this project to design the next one.
“To continue to build on the success and the scientific knowledge gained from this consortium, plans have been initiated for issuing new funding opportunity announcements,” said Birnbaum. “Please stay tuned.” Nadadur said announcements would be made in the near future.

“We’ve set the stage for pushing the ball forward for how people can ... produce tools that can be used in risk assessment,” said Justin Teeguarden, Ph.D., left, from the Pacific Northwest National Laboratory (PNNL). Gunter Oberdorster, D.V.M., Ph.D., right, from the University of Rochester, serves on the consortium’s external advisory committee. (Photo courtesy of Steve McCaw)
Even during breaks, scientists like Stephan Schwander, M.D., Ph.D., left, of Rutgers University, and Teresa Tetley, Ph.D., of Imperial College London, found time to continue to share insights and discuss the way forward. (Photo courtesy of Steve McCaw)

Nadadur, who designed and implemented the consortium project, pondered the advances made and the number of questions that still need to be answered in the interest of public health. (Photo courtesy of Steve McCaw)

Kian Fan Chung, M.D., D.Sc., of Imperial College London, discussed how health effects varied based on the shape of nanomaterials. For example, his team found that the inflammatory effect of exposure to silver nanowires was delayed compared with silver nanospheres. (Photo courtesy of Steve McCaw)

Return to Table of Contents
An NIEHS-led team solved a long-standing mystery about the origin of one of the cell types that make up the ovary. The team also discovered how ovarian cells share information during development of an ovarian follicle, which holds the maturing egg.

The scientists believe this new information on basic ovarian biology will help them better understand the cause of ovarian disorders, such as premature ovarian failure and polycystic ovarian syndrome — conditions that both result in hormone imbalances and infertility in women.

Technical advance reveals cell origins

Yao said that lineage tracing allowed him to follow the movement of a cell from its original birthplace to its eventual fate. The technique was not doable 10 years ago, but technological advances in genetics have made it possible. (Photo courtesy of Steve McCaw)

Liu did research as a graduate student in Yao’s lab before completing his doctorate. (Photo courtesy of Steve McCaw)

Without theca cells, women are unable to produce the hormones that sustain follicle growth, he continued. One of the major hormones theca cells produce is androgen, which is widely thought of as a male hormone. But, in a superb example of teamwork, the granulosa cells convert the androgen to estrogen.

Cell talk

As a result of their work, Yao and his colleagues uncovered the molecular signaling system that enables theca cells to make androgen. This communication pathway is derived from granulosa cells and another structure in the ovary called the oocyte, or immature egg cell. The crosstalk between the egg, granulosa cells, and theca cells was an unexpected finding, but one that may provide insight into how ovarian disorders arise.
“The problem starts within the theca cell compartment,” said Chang Liu, Ph.D., a visiting fellow in Yao’s group and first author on the paper. “Now that we know what makes these cells grow, we can search for possible genetic mutations or environmental factors that affect the process leading to ovarian cell disorders.”

For future work, Yao wants to explore the two types of cells that make up theca cells. Since the research has been carried out in mice, Yao will have to determine if the same holds true for humans, but the research may potentially uncover several roles theca cells play in female fertility.


Distinguished Lecture highlights circadian rhythms

By Robin Arnette

The May NIEHS Distinguished Lecture focused on circadian rhythms, or the changes most animals, plants, and microbes undergo in response to the light and dark cycles in an environment. John Hogenesch, Ph.D., from the University of Pennsylvania, has spent the past 15 years trying to understand how these clocks influence the physiology and behavior of organisms, particularly mammals. He shared highlights of his work May 15 in a presentation titled, “The Circadian Clock Network: Implications for Biology, Medicine, and Toxicology.”

The rhythm of life

Hogenesch began by explaining that most mammalian genes, including those important in toxicology, are under the control of a circadian oscillator, also known as a master clock. In humans, this clock is located in
a small part of the brain called the suprachiasmatic nuclei (SCN). Hogenesch explained that the human sleep pattern is the result of both the master clock, which controls the sleep and wake cycles, and the sleep homeostat, which measures the amount of sleep a person gets. This circadian network is reset each day by light striking special photoreceptor cells in the eye.

“Rods and cones are the two types of photoreceptor cells in the eye that form images, but melanopsin is a nonimaging photoreceptor that sends a light signal from the eye to the SCN,” Hogenesch said. “Inside each of the SCN neurons is a cell-specific clock that keeps biological time.”

Hogenesch emphasized the importance of these cycles. For instance, the majority of heart attacks occur between 8 a.m. and noon, and most people experience a drop in blood pressure of 15-30 percent during the night. Core body temperature, lung and muscle function, and other biological processes, including the dysfunction of cancer, depend on a working clock.

Members of the Hogenesch lab determined that approximately 55 percent of the mammalian genome is under clock control and will experience a surge in gene expression during a particular time within the 24-hour cycle. Surprisingly, they also found that tissues from the same animal may have different expression patterns. Most gene expression in the liver peaks around dawn, in anticipation of the next day, and lung genes peak in anticipation of the night phase. “In contrast,” Hogenesch said, “the kidney has a morning and evening rush hour.”

**Improving treatment of disease with chronotherapy**

According to Hogenesch, both the majority of genes associated with disease and the targets of medicines to treat those diseases are under clock control. Researchers have published hundreds of papers on chronotherapy, or the use of chemotherapeutics at various times of the day, to improve health treatments.

One example Hogenesch discussed was the use of statins to treat high cholesterol. Pioneers in the field discovered that cholesterol synthesis occurs at night in humans, so a pharmaceutical company ran clinical trials and told patients to take their medicine before bedtime. The statins had a short half-life, so they were still in the body and available to inhibit the target.

“We looked at the top 100 best-selling medicines in 2013, as well as the World Health Organization’s (WHO) list of the top 250 essential medicines,” Hogenesch said. “We found that 56 of the top 100 and a similar percentage of WHO drugs also had short half-lives and hit clock-regulated genes.”
In an effort to help other researchers find out if their favorite gene is regulated by the circadian clock, Hogenesch developed the **Circadian Expression Profiles Data Base**. He encouraged everyone in the audience to use the database in studies on how the circadian clock influences disease.

*Return to Table of Contents*

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**Gilbert sheds light on the microbiome and its invisible influence on health**

*By Deepa Singh*

The fascinating world of the microbiome and its influence on human health and disease was the topic of a May 7 Keystone Lecture Series talk by Jack Gilbert, Ph.D., from the University of Chicago and Argonne National Laboratory.

Gilbert brought his training as a microbial ecologist to bear, describing the microbiome as a sphere in which microorganisms interact with their environment, with each other, and with their hosts. “The bacterial world is fundamentally adapting to the environment in which it finds itself or is exposed to,” explained Gilbert. “It sees lot of changes around it, which are not very different from the changes it has seen throughout its evolutionary history.”

According to Gilbert, there are trillions of bacterial cells in our bodies, or two to three times more than the number of human cells. Better knowledge of the human microbiome is thus beneficial in understanding the therapeutic responses to clinical interventions.

**Microbes influence allergies and behavior**

Gilbert emphasized that microbes are present everywhere. “Therefore, every eukaryotic organism had to evolve mechanisms to deal with microbes, and the immune system is probably the key to this evolutionary process,” he said. By citing examples involving allergies to peanuts and cow’s milk, Gilbert demonstrated the importance of bacteria to autoimmune responses. In both cases, the addition of certain bacteria played a role in alleviating symptoms of the allergic response.

“The vast majority of the microbial biomass, about 2 to 3 pounds, is present in our intestine, and the rest of them are structured mostly around our skin, which is the largest organ in our body,” said Gilbert. (Photo courtesy of Steve McCaw)
According to Gilbert, microbes in the gut can also affect our brain function and may influence the risk of neurological disorders, including autism, anxiety, and depression. “Changing diet or adding microbes into the diet can drive the disordered phenotype or disordered microbiome back to the ordered one,” Gilbert said, referring to studies of maternal immune activation in mice. He also described studies in which fecal microbial transplants showed promising results for relieving symptoms of autism.

Biodiversity of microbes

People who work or live together are microbially more similar than the people who do not, and our built environment also affects these interactions with microbes, Gilbert said.

The Home Microbiome Study looked at the microbial diversity of a group of U.S. families over six weeks and found that humans alter the microbiome of a space when they occupy it. According to Gilbert, who led the study, every family that comes together shares their unique microbiome signature with the house.

Another of his projects, the Hospital Microbiome Study, set out to understand how microbial communities develop in a hospital. “Before the hospital was open, the microbial diversity was very low,” Gilbert said. “As soon as the hospital opened, it elevated, and the vast majority of the bacteria came from particles released from patients.”

Gilbert hopes these studies will increase scientific understanding of how microbial community structure is shaped by environmental factors. He emphasized that this would be important knowledge for the health care system, potentially leading to a reduction in disease outbreaks and antibiotic resistance.

Citations:


“Our Microbes, Ourselves”

By Kelly Lenox

Lisa Chadwick, Ph.D., presented the eighth Big Picture, Small Talk on May 6, highlighting the human microbiome and its contribution to health. “Microbes coat any surface of your body — inside and out — that they can,” Chadwick said in her talk, “Our Microbes, Ourselves.” The audience came from all divisions of the institute.

Chadwick listed some of the useful jobs microbes perform:

- Helping digest foods, making essential nutrients available.
- Synthesizing chemicals that our bodies cannot make.
- Increasing available amounts of chemicals we do make, such as serotonin.
- Helping develop the immune system.
- Protecting the body from dangerous bacteria, known as pathogens.

Although the kinds and amounts of bacteria at a given body site may differ from one person to another, Chadwick explained that those microbes generally perform a similar set of biological functions. Normal life events, including fever, antibiotics, and dietary changes may temporarily alter a person’s microbiome, but it will usually return to its normal state. She cautioned that widespread use of antibacterial soap and other personal products containing antimicrobial agents may also affect our microbiome.

Researchers are beginning to associate certain diseases with changes in the microbiome, according to Chadwick. “But the field is still new enough that we don’t have a lot of examples showing cause and consequence,” she said.

Chadwick also discussed NIEHS-funded studies related to the microbiome, such as the effects of arsenic exposure. The effects may work both ways, she said, in that the microbes may metabolize the contaminant, and at the same time, the contaminant may affect the makeup of the microbiome.

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

Return to Table of Contents

Andres awarded EMM New Investigator Best Paper

By Qing Xu

Sara Andres, Ph.D., visiting fellow in the Genome Stability Structural Biology Group led by Scott Williams, Ph.D., received the 2014 New Investigator Best Paper Award from the Environmental Mutagenesis and Genomics Society (EMGS), in late April.

The editorial board of the society’s journal, Environmental and Molecular Mutagenesis, earlier chose Andres’ paper, “Recognition and Repair of Chemically Heterogeneous Structures at DNA Ends,” as the Editor’s Choice article, when it was published in the January 2015 issue.

EMGS was founded in 1969 to provide support to scientists in the field of environmental mutagenesis. The award includes a $250 cash prize, free registration to the 2015 annual meeting, and a one-year membership in the society.

Great exposure for a new team

Lead author Andres said the award reflects the work of the whole lab, which investigates DNA damage and repair. “The award is the result of a full team effort,” Andres said. “Every author on that paper contributed to the end result, so the award is really a reflection of the amazing people I get to work with every day. Scott’s lab is relatively new, so to be able to garner recognition for our work is great exposure for all of us.”

According to Andres, EMGS invited Williams to write a review, so the paper addresses one of the lab’s main focus areas — discovering how damaged DNA ends are resolved in cells. “Sara has done excellent work here studying the role of the Ctp1 protein in DNA repair, so I asked her to take the lead on the review article,” said Williams.

DNA breaks, whether spontaneous or induced by stressors, such as radiation and chemicals, are like a chemical mess that needs to be cleansed before they can be properly repaired, Andres explained. So the paper provides an extensive overview of cellular responders that detect and repair the heterogeneous DNA ends.

Andres is looking forward to attending the 2015 EMGS conference and sharing her work with a larger audience. (Photo courtesy of Steve McCaw)

Williams, who holds a secondary appointment in the Signal Transduction Laboratory, studies the mechanisms through which DNA breaks are recognized and repaired in cells. (Photo courtesy of Steve McCaw)
“We hope the paper will provide another perspective on DNA damage and become a reference point for professors in a classroom, new graduate students learning about the DNA repair field, or any researcher wishing to know more about resolution of DNA damage,” she said.

Andres received her Ph.D. from McMaster University in Canada, where she studied DNA repair and structure-function with Murray Junop, Ph.D. “I have been very fortunate to continue studying DNA repair at NIEHS, where I am surrounded by leading experts in my field,” she said.


(Qing Xu is a biologist in the NIEHS Metabolism, Genes, and Environment Group.)

Return to Table of Contents

**Expert panel identifies research needs on high folic acid intake**

*By Robin Mackar*

The National Toxicology Program (NTP) and the National Institutes of Health (NIH) Office of Dietary Supplements (ODS) convened an **expert panel** to identify research needs related to high intakes of folic acid.

The panel was asked to review scientific literature on the topic, after studies suggested that consuming high levels of folic acid may be associated with potential adverse health effects. At a May 11-12 meeting in the NIH Natcher Conference Center in Bethesda, Maryland, the panel made recommendations in four health areas, to help guide future research.

**Setting the stage**

NIEHS and NTP Director Linda Birnbaum, Ph.D., and NTP Associate Director John Bucher, Ph.D., welcomed participants. Meeting chair **Cutberto Garza, M.D., Ph.D.**, from John Hopkins University, introduced three presenters who provided the context for the evaluation.

**Gary Shaw, Dr.P.H.,** from Stanford University, presented an epidemiological perspective on the important role that folic acid plays in preventing birth defects. Folic acid is a B vitamin that helps the body’s cells grow and divide. He reviewed well-established research demonstrating that the risk of neural tube defects in infants can be lessened if women take folic acid before getting pregnant and during early pregnancy. Shaw said it is unclear how it prevents the defects, but that folic acid supplementation has been a clear success story.

**Nutritional epidemiologist Regan Bailey, Ph.D.,** with ODS, discussed folic acid sources and supplement use. She cited ready-to-eat cereal, yeast bread, rolls, and pasta as some of the main food sources. There is very little folic acid deficiency in children or adults in the U.S., Bailey said, but about 65 percent of children have high folate levels, as do 60 percent of adults. Folic acid is the synthetic form of folate and is used in fortified foods.
and supplements. Folate occurs naturally in food. According to Bailey, the upper limit for folic acid intake set in 1998 by the Institute of Medicine is 1000 micrograms per day. The recommended daily allowance is 400 micrograms per day.

Christine Pfeiffer, Ph.D., of the Centers for Disease Control and Prevention, described three laboratory methods used most often to assess levels of folate in blood. She discussed the pros and cons of each and discussed the assays, or tests, used in the National Health and Nutrition Examination Survey (NHANES) across the years and explained how conversions were made when assays were changed.

**Expert subpanels**

After the morning talks, the experts divided into subpanels to address the four major health effects that emerged from a comprehensive literature search conducted by staff from the NTP Office of Health Assessment and Translation. These included cancer, cognition in conjunction with vitamin B12 deficiency, hypersensitivity-related outcomes, and thyroid and diabetes-related disorders.

Abee Boyles, Ph.D., lead NTP scientist for the project, explained the literature review process and how the major health effects were determined. The panel members deliberated throughout the afternoon and into the evening, and approved a lengthy list of research recommendations the following day.

Although the experts were not asked to rank their recommendations, a few priority areas emerged. The cancer group, for example, discussed the need for more studies of cancer growth, especially in vulnerable populations and at different stages of life. The cognition group discussed the need for a meta-analysis of human studies, with additional studies to look at the biological mechanisms behind cognitive impairments related to high folic acid use in people with vitamin B12 deficiency.

The hypersensitivity group found little concern in the current literature on respiratory infection and eczema. Also, the diabetes and thyroid group had little concern about increased diabetes risk from high folic acid intake.

NTP has made available a full list of the recommendations and will issue a monograph on the topic.

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

*Return to Table of Contents*
GEMS meeting showcases new genetic research funded by NIEHS

By Eddy Ball

The role of genetic variation in shaping host response to environmental exposures was the focus of the Genetics and Environmental Mutagenesis Society (GEMS) Spring Meeting.

Attendees gathered on April 27 at the U.S. Environmental Protection Agency (EPA) conference center in Research Triangle Park, North Carolina, to learn about new developments in work by four local research groups funded by NIEHS. The featured scientists use systems genetics approaches in mice and flies, and genome-wide association studies (GWAS) in humans, to analyze quantitative traits.

GEMS President and EPA senior scientist Channa Keshava, Ph.D., presented opening remarks before handing the program over to GEMS President-elect and program chair Stephanie Smith-Roe, Ph.D., a genetic toxicologist with the National Toxicology Program (NTP).

Mice bred for genetic diversity create a more informative model

Smith-Roe introduced retired NTP toxicologist Jef French, Ph.D., who led efforts to use a new mouse model population for improved studies of chemical toxicity. Using the model known as Diversity Outbred (DO) as one component of the Tox21 program, researchers will be able to test chemicals prioritized by high-throughput screening far more effectively than is possible with the traditional approach, which uses one strain of mouse and one strain of rat in a two-year assay.

According to French, the DO mice, which are derived from outcross breeding of 175 Collaborative Cross (CC) pairs, more closely resemble the diversity in human populations compared with the genetic uniformity in traditional lab animal lines (see related story). “Each [mouse] is genetically different from the others,” he said.

A thematically consistent, but operationally distinct approach, was presented by University of North Carolina at Chapel Hill (UNC) geneticist Samir Kelada, Ph.D. Kelada is an NIEHS Outstanding New Environmental Scientist awardee who uses the CC mouse model for studying the genetics of environmentally induced airway disease.

GEMS fall 2015 meeting – Mark the calendar

GEMS will hold its annual showcase meeting Oct. 28 at the North Carolina Biotechnology Center in Research Triangle Park, North Carolina. Keynote talks will explore the theme, “The Impact of Environmental Exposures on Genomic Health Across Generations.”

The all-day event will feature presentations by leading scientists; a poster competition and short talks by students and postdoctoral fellows; and awards for best talk and poster presentations.

Featured speakers will be EPA senior scientist David DeMarini, Ph.D.; Carlton University and Health Canada biologist Carole Yauk, Ph.D.; NIEHS Deputy Director Rick Woychik, Ph.D.; and geneticist Folami Ideraabdullah, Ph.D., of the UNC Nutrition Research Institute.
Building on well-established paradigms

“Everything old is new again” could easily have been the subtitle of the talk by geneticist Trudy MacKay, Ph.D., from North Carolina State University. MacKay’s team is working to define the intricate genetic architecture of environmental sensitivity in fruit flies.

Although fruit flies are a long-established model, MacKay’s innovation is an intensive multigenerational inbreeding program involving flies from a very specific location — the Raleigh, North Carolina farmers’ market. In addition to studying gene-environment interactions, the researchers are tracing the interaction networks of common genes. “It turns out to be more complicated that we thought,” she said.

The program concluded with a presentation of results from large-scale human studies by NIEHS molecular epidemiologist Stephanie London, M.D., Dr.P.H., “Smoking and the Epigenome Across the Lifecourse.” In a landmark 2012 study, London’s group used a new, specialized tool for assessing epigenetic modifications from DNA methylation.

The team then conducted GWAS and identified several novel genes specific to tobacco smoke detoxification and other development processes in more than 1,000 pregnant mothers and their offspring from a Norwegian cohort (see story). Their results were validated in separate studies by other groups, and London’s group is now participating in even larger scale, multicohort studies.

(Eddy Ball is a contract writer for the NIEHS Office of Communications and Public Liaison)
Biostatistician David Umbach, Ph.D., center, was among NIEHS scientists in attendance. GWAS studies involve an immense amount of data and routinely include statisticians as co-authors. (Photo courtesy of Steve McCaw)

Each of the speakers received a token of appreciation from GEMS. Shown, left to right, are Smith-Roe, London, and Keshava. (Photo courtesy of Steve McCaw)

Along with active scientists from NIEHS, EPA, and local universities, the audience included retired NTP toxicologist Barbara Shane, Ph.D., left, and retired NIEHS scientist Errol Zeiger, Ph.D., J.D. (Photo courtesy of Steve McCaw)

An NIEHS grantee, MacKay holds an appointment as a distinguished professor and her long list of honors includes election to the National Academy of Sciences, and being named a Fellow of the United Kingdom’s Royal Society. (Photo courtesy of Steve McCaw)

Biostatistician David Umbach, Ph.D., center, was among NIEHS scientists in attendance. GWAS studies involve an immense amount of data and routinely include statisticians as co-authors. (Photo courtesy of Steve McCaw)

Return to Table of Contents
NIEHS celebrates core support on Genomics Day

By Eddy Ball

As the data get bigger and the technology grows increasingly sophisticated, it is becoming more critical for NIEHS to maintain its network of core support for genomics research. At this year’s Genomics Day, May 7, the institute’s scientists gathered to learn about the constantly growing scope of resources available to help research teams explore entire genomes and interpret their findings.

“Every year it gets more and more interesting,” observed moderator Kevin Gerrish, Ph.D., in his introduction. He has chaired the event since its beginning in 2009.

Exploring the potential of new tools

Gerrish explained that the cores at NIEHS receive cross-divisional funding to provide equipment and expertise that individual research groups could not supply on their own. These include the latest in instrumentation, such as the newly acquired NanoString Technologies nCounter Analysis System, and specialized assistance in experiment design and data interpretation.

In addition to the overview by Gerrish, who is acting director of the Molecular Genomics Core, attendees heard from lead researcher Paul Wade, Ph.D., who heads the Epigenomics Core, and David Fargo Ph.D., director of the Integrative Bioinformatics Core.

Wade spoke of numbers that ranged as high as 13 billion — the total number of reads performed on sequencing instrumentation over the past two years. Fargo described his group’s high performance computing capabilities — 2 terabytes, or nearly two trillion bytes, of random access memory and 1.3 petabytes, or more than one quadrillion bytes, of data storage.

Seeing core support in action

Trainees gave a series of six short talks illustrating outcomes of research supported by the cores. This allowed the trainees, representing NIEHS and the National Toxicology Program (NTP), to present the latest results of their work, ranging from studies of memory storage at the molecular level to explorations of the mechanics of epigenetic modification of gene expression.

The keynote talk was given by distinguished lead researcher Thomas Kunkel, Ph.D., head of the DNA Replication Fidelity Group. Kunkel presented an overview of the essential process of error correction, which the genome constantly performs in every cell of the body with mind-boggling speed and near perfect accuracy. He also explained what happens when the genome’s safety net fails, leading to serious and even life-threatening diseases, including cancer.
Kunkel, who is a leading authority on replication processes, demonstrated how whole genome sequencing of yeast allowed his team to analyze replication error rates in 8 diploid yeast strains over 900 generations. He said he expects the findings from the 12 million base-pair yeast genome to parallel findings anticipated from research underway on the human genome, which is 250 times as large.

The day concluded with a poster session, presented by institute researchers, NIEHS core representatives, and 15 participating vendors.

**Leveraging institute-wide resources**

Although Genomics Day presentations highlighted sequencing and bioinformatics support, several researchers took advantage of other resources from across the institute, including the Flow Cytometry Core and Clinical Research Unit. The trainees who presented are:

- **Shannon Farris, Ph.D.** — Farris S, Wang Y, Ward JM, Dudek SM. “Plasticity in Hippocampal Area CA2: Lost in Translation?”


- **Thuy-Ai Nguyen, Ph.D.** — Nguyen T-A, Menendez D, Grimm SA, Bushel PR, Ward JM, Freudenberg JM, Jothi R, Fargo DC, Resnick MA. “P53 Binding and Regulation of Immune Response Genes in Human Primary T-lymphocytes.”


- **Janine Santos, Ph.D.** — Lozoya O, Grenet D, Wolfgang T, Santos J, Woychik R. “Crosstalk Between Mitochondrial Function, the Epigenome, and Gene Expression.”

- **Benjamin Scruggs, Ph.D.** — Scruggs BS, Gilchrist DA, Nechaev S, Muse GW, Burkholder A, Fargo DC, Adelman K. “Upstream Anti-sense Promoters Are Distinct Hubs of Transcription Factor Binding and Active Histone Modifications.”
Kunkel’s presentation illustrated the value of core support in unraveling the mysteries of DNA replication fidelity in health and disease. He and his collaborators demonstrated that the type of errors in replication vary among the three polymerases involved in humans — alpha, delta, and epsilon. (Photo courtesy of Steve McCaw)

Chan, left, listened to NTP toxicologist June Dunnick, Ph.D., as she outlined molecular changes in mice exposed to dimethylpropiolothetin, a chemical used in medical devices. She said these changes represent candidate markers for nasal cavity environmental toxins linked to cancer progression. (Photo courtesy of Steve McCaw)

Wade, left, chatted with contractor Ruchir Shah, Ph.D., who is involved in NTP high-throughput screening and co-authored one of the poster studies. (Photo courtesy of Steve McCaw)

NIEHS biologist Yin Li, Ph.D., left, explains the results of her team’s whole-transcriptome expression profiling to staff scientist Harriet Kinyamu, Ph.D. (Photo courtesy of Steve McCaw)

(Eddy Ball is a contract writer for the NIEHS Office of Communications and Public Liaison)

Return to Table of Contents
This month in EHP

The June issue of Environmental Health Perspectives (EHP) examines the complex relationship between climate change and air pollution.

Air Quality and Climate Change: A Delicate Balance
Dust, allergens, soot, water vapor, and other particles and gases in the atmosphere are constantly interacting and forming new mixtures, often with the influence of heat and ultraviolet radiation. Many direct human health effects of these airborne agents have been well characterized. Some of these agents also have greenhouse properties, contributing to the overall warming of the planet, while others impart cooling effects. Climate change and air pollution are thus inextricably intertwined.

Research summaries featured this month include:

• **Pediatric Vaccines and Neurodevelopment: Primate Study Finds No Adverse Behavioral Effects** — Authors of a detailed study of neurodevelopment, learning, and social behavior in macaques report no adverse developmental or behavioral effects associated with the full pediatric vaccine schedule.

• **Comparing BPS and BPA: Cardiovascular Effects in Female Rat Hearts** — A research team that reported impacts of bisphenol A (BPA) on the female rat cardiovascular system now report nearly identical impacts from exposure to bisphenol S (BPS), which is often thought to be a safer alternative to BPA.

• **Exercise and Air Pollution: Study Suggests Benefits Outweigh the Health Risks of NO2 Exposure** — Scientists found that over the long term, exposure to air pollution while exercising did not appear to reduce the beneficial health effects of physical activity.

• **Examining Mixtures of Disinfection Byproducts: Rat Study Shows No Effects on Reproduction** — Researchers report on the reproductive effects, in rats, of a mixture of disinfection byproducts that can form when water treatment chemicals interact with other compounds in water.

*Return to Table of Contents*

**Extramural papers of the month**

*By Nancy Lamontagne*

• Reduced air pollution during Beijing Olympics linked with higher birth weights

• Early exposure to arsenic decreases lung function in children

• How alpha-synuclein causes Parkinson’s-associated neural damage

• BPA exposure shows transgenerational effects on reproductive health

*Read the current Superfund Research Program Research Brief. New issues are published on the first Wednesday of each month.*
Reduced air pollution during Beijing Olympics linked with higher birth weights

NIEHS grantees report that women who were in their eighth month of pregnancy during the 2008 Beijing Olympics, when the Chinese government implemented policies to reduce air pollution levels, gave birth to children with higher birth weights compared to women pregnant before or after the games.

The air pollution controls implemented during the Beijing Olympics lasted for 6 to 7 weeks and were then relaxed, creating a natural experiment in which to study air pollution effects. The controls resulted in a 60 percent reduction in sulfur dioxide, 48 percent reduction in carbon monoxide, 43 percent reduction in nitrogen dioxide, and a reduction in particulate matter less than 2.5 microns in diameter (PM2.5).

The researchers examined birth records from 83,672 full-term babies born to mothers in four urban Beijing districts. They found that babies whose eighth month of pregnancy occurred during the Beijing Olympics were on average 23 grams larger than those with their eighth month of pregnancy falling in the same dates in 2007 and 2009. The researchers observed that interquartile range increases in concentrations of PM2.5 (19.8 micrograms per cubic meter), carbon monoxide (0.3 parts per million), sulfur dioxide (1.8 parts per billion), and nitrogen dioxide (13.6 ppb) during the eighth month of pregnancy were associated with 18g (95% CI: -32g, -3g), 17g (95% CI: -28g, -6g), 23g (95% CI: -36g, -10g), and 34g (95% CI: -70g, 3g) decreases in birth weight, respectively. No significant associations were seen for pregnancy months one through seven.


Early exposure to arsenic decreases lung function in children

An NIEHS grantee and colleagues report that in utero and early life exposure to arsenic through drinking water was associated with decreased lung function in children. Although several studies have reported more respiratory symptoms and diseases in people highly exposed to arsenic through drinking water, this is one of the first studies to look at early life arsenic exposure and lung function in children.

The researchers assessed the urinary concentrations of inorganic arsenic in 358 healthy children exposed to average arsenic concentrations of 152.13 micrograms per liter from pregnancy until early childhood. The urinary arsenic level among the participants averaged 141.2 micrograms per liter, and only 16.7 percent of the children had a urinary concentration below the national concern level.

The children in the study showed a reduced forced vital capacity — the maximum amount of air a person can expel from the lungs after a maximum inhalation — that was negatively associated with the percentage of inorganic arsenic. More than 57 percent of the children in the study showed a restrictive spirometric pattern, which indicates how quickly and effectively the lungs can be emptied and filled. The urinary arsenic levels were higher in children with restrictive lung patterns compared to study participants with normal spirometric patterns.

Based on these results, the researchers say that controlling exposure to arsenic during critical early life lung development may be important for reducing deficits in lung function.
How alpha-synuclein causes Parkinson’s-associated neural damage

New research, funded in part by NIEHS, has revealed key insights into how alpha-synuclein aggregates cause damage to neurons in diseases such as Parkinson’s disease. The research also revealed a possible new therapeutic strategy that might prevent the progressive neuron loss of Parkinson’s disease.

In Parkinson’s disease, alpha-synuclein aggregates released from neurons activate immune cells known as microglia, leading to chronic neuroinflammation that damages neurons. Using cultured rat cells, the researchers conducted experiments to find out more about how alpha-synuclein affects microglial activity. They also studied why microglia migrate toward injured neurons and tend to accumulate with alpha-synuclein aggregates in the affected areas of Parkinson’s disease brains, such as the substantia nigra.

The experiments showed that neuron-derived alpha-synuclein aggregates act as chemoattractants that direct microglial migration by acting on NADPH oxidase and several downstream proteins. Blocking the targets involved in alpha-synuclein–mediated microglial directional migration could protect against progressive neuronal loss, representing a potential therapeutic strategy for Parkinson’s disease and other diseases involving alpha-synuclein aggregates.


BPA exposure shows transgenerational effects on reproductive health

A study, funded in part by NIEHS, found an association between low levels of BPA exposure during pregnancy and reproductive problems in the next three generations of mice. The new findings suggest that some effects of in utero BPA exposure, including the ability to become pregnant and maintain pregnancy to term, may be transgenerational.

The researchers exposed pregnant mice to BPA levels equivalent to those considered safe in people from gestation day 11 until they gave birth. This exposure was associated with significant reproductive problems, including declines in fertility, sexual maturity, and pregnancy success, in three generations of female mouse offspring. The first generation of pups also experienced an abnormal estrous cycle and engaged less in typical mating behavior than mice not exposed in the womb. The third generation, which was not directly exposed to BPA either as a fetus or as an egg in a fetus in its mother’s womb, experienced later sexual maturity, reduced fertility, and lower pregnancy success than mice whose ancestors were not exposed to BPA. In the third generation, the lowest dose of BPA (experienced by their great-grandmothers) interfered most with their fertility.

The researchers say that future studies should investigate the mechanism underlying the effects of BPA on female reproduction outcomes in the first to third generations of offspring.
Intramural papers of the month

By Greg Buchold, Deacquinta Diggs, Gabriel Knudsen, Vijay More, and Shannon Whirledge

• NTP finds that arsenic induces multiple cancer characteristics in lung cell model
• Mammalian milk secretion uses novel mechanism
• The origins of the ovarian theca cells
• New biomarkers could screen endocrine-disrupting chemicals
• Long repetitive sequences drive some types of mutations

NTP finds that arsenic induces multiple cancer characteristics in lung cell model

Researchers in the National Toxicology Program (NTP) used inorganic arsenic to convert human peripheral lung epithelial (HPL-1D) cells into cells with characteristics of cancer. The work suggests that low-level arsenic exposure may directly induce changes in lung epithelial cells that could lead to adenocarcinomas. The model may be useful in studying the mechanisms of arsenic-induced lung cancer.

After 38 weeks of arsenic exposure, HPL-1D cells developed some characteristics of cancer cells, including secreting enzymes common in cancer cells, growing in serum-free medium and forming colonies, and reducing the protein expression of tumor suppressor genes. Once the cells reached this stage, the researchers renamed them chronic arsenic-treated lung epithelia (CATLE) cells.

Epithelial-to-mesenchymal transition (EMT) occurs in cells as they change into cancer cells. CATLE cells exhibited a decrease in the EMT marker protein, e-cadherin, while the metallothioneins MT1A and MT2A, and the oxidative stress response genes HMOX1 and HIF1A, increased in response to arsenic exposure.

This research is consistent with work from other groups that suggests lung adenocarcinomas likely arise from the epithelia of peripheral lung tissue. Although additional cell models are needed, this model may be used to explore arsenic-induced lung cancer. (DD)


Return to Table of Contents
Mammalian milk secretion uses novel mechanism

According to scientists from NIEHS and several other academic institutions, Orai1, a calcium channel subunit, is responsible for delivering 50 percent of the calcium ions present in mammalian milk, and for signaling milk secretion through mammary cell contractility. The finding that Orai1 is required for milk ejection redefines how the process is thought to occur. The report describes this important mechanism behind the process of lactation.

Using genetically modified mice, the research team found that mice lacking Orai1 produced milk containing low concentrations of calcium. They also captured the pulsating contractions of the mammary alveoli and quantified the dependency of alveoli cells on Orai1, using state-of-the-art 3-D imaging technology. Alveoli from mice without Orai1 exhibited infrequent contractions, were less responsive to oxytocin, and were less coordinated.

These data demonstrate that calcium ions play a role in cellular signaling greater than being simply a nutritional component. The novel role of Orai1 channels in alveolar contractility also suggests the possibility of their involvement in the function and dysfunction of other exocrine tissues, including sweat glands. (VM)


Return to Table of Contents

The origins of the ovarian theca cells

NIEHS researchers and collaborators have discovered the origins of the steroid-producing theca cells in the ovary, as well as the signaling pathways involved in cell fate specification and differentiation of the theca cell. During development, the ovary establishes follicles, consisting of the oocyte surrounded by granulosa and theca cells. This basic unit represents the foundation of mammalian reproduction, and dysfunction in any one of these cell types can result in infertility.

Using an inducible lineage-tracing model, the authors show that adult theca cells stem from two distinct progenitor populations — one from the fetal ovary and the other from early embryonic tissue, called mesonephros. These two populations are present in the adult ovary at different numbers and maintain a lineage-specific transcriptome. Ovary-derived theca cells exhibit higher expression of genes implicated in cell growth and proliferation, while those derived from the mesonephros are enriched for genes that regulate steroidogenesis.

Regardless of their origin or adult function, the same signaling pathway is responsible for theca cell differentiation from the two populations. Components of the Hedgehog signaling pathway, Indian hedgehog (Ihh) and Desert hedgehog (Dhh), which are critical to normal embryonic development, induce expression of Gli1, the marker of progenitor theca cells. The production of Hedgehog signals from the granulosa cells is achieved through oocyte-derived factor, indicating that theca cell development in the ovary is a result of the coordinated signaling between many cell types. Understanding the complex, multicellular process in which theca cells arise may shed light on disorders resulting from aberrant theca cell development, such as polycystic ovary syndrome and premature ovarian failure. (SW)

Citation: Liu C, Peng J, Matzuk MM, Yao HH. 2015. Lineage specification of ovarian theca cells requires multicellular interactions via oocyte and granulosa cells. Nat Commun6:6934. (Story)

Return to Table of Contents
New biomarkers could screen endocrine-disrupting chemicals

A research team led by NIEHS scientists has identified a group of more than 100 genes capable of identifying endocrine-disrupting chemicals (EDCs), which are compounds that interfere with the hormone system of an organism. Using these genes as biomarkers could not only help uncover the mechanisms that EDCs use to impact public health, but could also serve as a secondary screen for the Tox21 high throughput project at NTP.

EDCs can behave like naturally occurring estrogens, negatively altering the balance of signaling pathways that are normally triggered by estrogen. The researchers tested the estrogenic effects of substances on mouse uterine tissue by measuring the increase of DNA synthesis in epithelial cells. At the end of 24 or 72 hours of treatment, they evaluated the weight of uterine tissue and used the data to indicate whether the estrogenic substance was long-acting, which resulted in a weight increase, or short-acting, which brought little or no weight increase.

Using microarrays and computational tools the scientists analyzed how long-acting or short-acting estrogens impact thousands of genes in the uterus. They selected more than 100 genes to use as a biomarker panel to distinguish chemicals that mimicked long-acting (estradiol or diethylstilbestrol) versus short-acting (estriol) estrogens. The novel chemical diarylheptanoid D3, derived from a plant in the ginger family used by postmenopausal women in Thailand, was identified through the assay as a short-acting xenoestrogen similar to bisphenol A and HPTE. (GB)


Return to Table of Contents

Long repetitive sequences drive some types of mutations

NIEHS researchers have demonstrated that insertion-deletion, or indel, mutation rates increase 100,000-fold with increasing homonucleotide run length, using yeast strains with combinations of defects in their mismatch repair (MMR) machinery and DNA polymerases. Such runs play important roles in chromatin organization, gene expression, and chromosome replication. Mutation rates are used to calibrate molecular clocks, assess human tumors, and identify genetic variants in human diseases. Prior to this research and the work of other NIEHS scientists, many researchers assumed the rates were similar across the genome.

These small indels, driven by DNA strand slippage during replication, are usually repaired by both MMR and exonucleolytic proofreading (PR). MMR defects allowed indels, especially in long DNA repeat tracts, which are the source of the microsatellite instability that is a hallmark of MMR-defective tumors. In contrast, the researchers showed that PR defects selectively increase indel rates in short repeat tracts. These data are especially useful given that coding sequences contain higher proportions of short tracts than noncoding regions of DNA, leading to the accumulation of more coding mutations, with likely ultimate outcomes of disease or carcinogenesis. Should the indel pattern hold in future studies of tumors containing PR defects, indels in short runs could be diagnostic in the way that microsatellite instability is for mismatch repair-defective tumors. (GK)

Citation: Lujan SA, Clark AB, Kunkel TA. 2015. Differences in genome-wide repeat sequence instability conferred by proofreading and mismatch repair defects. Nucleic Acids Res 43(8):4067-4074.
(Greg Buchold, Ph.D., is a former NIEHS postdoctoral fellow in the Reproductive and Developmental Biology Laboratory. Deacqunita Diggs, Ph.D., is a National Health and Environmental Effects Laboratory fellow in the U.S. Environmental Protection Agency Developmental Toxicity Branch. Gabriel Knudsen, Ph.D., is a research fellow in the National Cancer Institute Center for Cancer Research Laboratory of Toxicology and Toxicokinetics. Vijay More, Ph.D., is a former visiting fellow in the NIEHS Intracellular Regulation Group. Shannon Whirledge, Ph.D., is an Intramural Research Training Award fellow in the NIEHS Molecular Endocrinology Group.)

Return to Table of Contents
Health and Fitness Week returns to NIEHS

By Ian Thomas

May 4 marked the start of Health and Fitness Week at NIEHS, a fun-filled event held annually to promote exercise, nutrition, and wellness among institute employees and contractors.

Widely seen as an unofficial rite of spring, the 2015 schedule offered a full slate of favorites, such as the table tennis and 3-on-3 basketball tournaments, plus a handful of new events, including the Zumba Dance Party.

Something for everyone

“The goal of Health and Fitness Week has always been to show our employees how much fun it is to get out of the office and be active,” said VeeVee Shropshire, a member of the NIEHS Office of Management Health, Fitness, and Wellness Work/Life Balance Organizing Committee (see text box). “Coming into 2015, we wanted to create a balanced schedule that anyone could take part in, and I think we really succeeded in doing that.”

Another new event for 2015 was the Ping Pong How-to Clinic, led by NIEHS biologist Frank Chao, Ph.D., which kicked off the week.

“Frank took us through a quick rundown of the rules of ping pong then gave us our space to practice different types of serves and hits,” said NIEHS management analyst Claire Long, one of the coordinators of this year’s events. “It was a lot of fun, in addition to being a low-key, low-pressure introduction to a highly fast-paced game.”

Shropshire took a shot at the basketball shootout. (Photo courtesy of Steve McCaw)

2015 Health and Fitness Week activities

**Monday, May 4** — Ping Pong Clinic, Employee Assistance Program Seminar, Table Tennis Tournament

**Tuesday, May 5** — “Alden” Basketball Shootout (men and women), Zumba Dance Party, Table Tennis Tournament, Fitness Center Equipment Demos

**Wednesday, May 6** — Beanbag Toss Competition, 3-on-3 Basketball Round-robin, Table Tennis Tournament

**Thursday, May 7** — 2-mile Nature Walk and Run, Football Throw, Table Tennis Tournament

**Friday, May 8** — Employee Golf Outing
As always, the 2-mile Nature Walk and Run ranked among the week’s most popular activities. Set to a backdrop of sunny skies and temperatures in the low 70s, the event drew more than two dozen participants for a leisurely stroll around Discovery Lake.

“Honestly, with weather like this, who wouldn’t want to get out of the office for a quick run?” joked Kimberly Peterson, a longtime employee at NIEHS.

Health and Fitness Week takes place during National Physical Fitness and Sports Month, an observance designated by presidential proclamation.

(Ian Thomas is a public affairs specialist in the NIEHS Office of Communications and Public Liaison and a regular contributor to the Environmental Factor.)
In addition to her duties in the Office of Management, Long works with the NIEHS Fitness Room. (Photo courtesy of Steve McCaw)

Gorgeous weather added to the enjoyment of the Nature Walk and Run. (Photo courtesy of Steve McCaw)
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