National Institute of Environmental Health Sciences

Environmental Factor

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March 2015

NIEHS Spotlight

NIEHS highlights public health and disaster research at oil spill conference

Five years after the Deepwater Horizon disaster, NIEHS joined researchers from across the globe to share results at the Houston conference.

Sandler honored by AMA for outstanding government service

Dale Sandler, Ph.D., head of the NIEHS Epidemiology Branch, is the recipient of a Dr. Nathan Davis Award for Outstanding Government Service.

Assessing alternatives to substances that present exposure risk

Joel Tickner, Ph.D., gave an energetic talk on alternatives assessment, a process to ensure alternatives are safer than substances they are meant to replace.

NIEHS funds six early-career researchers for innovative science

New grants totaling $3 million will go to six outstanding early-career scientists, bridging the funding gap to independent biomedical research.

Miller receives Target ALS award to study therapy for Lou Gehrig's disease

In January, NIEHS lead investigator David Miller, Ph.D., received a three-year grant to improve therapeutic drug delivery for treating amyotrophic lateral sclerosis.

Clinical Feature

The Precision Medicine Initiative Video

President Obama announced a funding commitment for the Precision Medicine Initiative, to develop individually tailored medical treatments.

Science Notebook

NIEHS-supported researchers map epigenome of more than 100 tissue and cell types Video

The Nature journals published 20 papers from the NIH Roadmap Epigenetics Mapping Consortium, with epigenome maps of 111 cell types.

Epigenetics workshop features wide range of cutting-edge research

The Jan. 23 cross-divisional minisymposium featured NIEHS scientists and grantees sharing their latest research and inspiring collaborations.

NIEHS-NCI collaboration leads to novel analysis of anticancer therapeutics

NIEHS scientists, collaborating with the National Cancer Institute, used a novel toxicogenomics approach to predict toxicity risks of combination anticancer therapies.

NIEHS Spotlight

Environmental exposure research and public policy

Tracey Woodruff, Ph.D., discussed the value of testing for mixtures of chemicals and using scientific data to influence policy in a Feb. 2 talk.

New RESTORE Act center builds on NIEHS experience

A new center, created with funds from the Deepwater Horizon oil spill, is headed by leaders of two NIEHS Centers of Excellence in Texas.

Linking high-throughput data to human exposures

More than 250 viewers learned about methods to extrapolate *in vitro* data to *in vivo* dose levels in a Jan. 27 NICEATM webinar.

NIEHS fellow to receive achievement award at upcoming SOT conference

Erin Quist, D.V.M., will receive the Roger O. McClellan Student Award for her proposed presentation at the 2015 Society of Toxicology conference in March.

Occupational health insights into environmental exposures

Occupational medicine specialist Manijeh Berenji, M.D., offered insights into preventing and treating environmental exposures.

SRP network helps parents understand vapor intrusion in schools

NIEHS-funded experts on vapor intrusion joined a meeting to educate communities of two schools located over contaminated groundwater.

Science Notebook

Seminar highlights emerging biomarkers of inflammation

The NIEHS Cross-Divisional Inflammation Faculty seminar addressed the role of biomarkers in treating heart and lung disease.

Study adds to understanding of respiratory syncytial virus disease

A new study, funded in part by NIEHS, offers insight into the network of mechanisms involved in triggering a life-threatening respiratory disease in infants.

Researcher explores neuro-behavioral effects of endocrine disruption

Grantee Andrea Gore, Ph.D., energized her audience Jan. 30 at NIEHS with her talk on “Environmental Endocrine Disruption of the Brain: Past, Present, and Future.”.

NTP presents SAN trimer results at Toms River public meeting

NTP shared results of SAN trimer studies, which found no carcinogenicity, with residents near the Toms River Superfund site in New Jersey.

Yakel engages audience at Duke toxicology seminar

NIEHS neurobiologist Jerry Yakel, Ph.D., discussed neuronal excitability and plasticity, particularly the response to nicotine.

This month in EHP

The March issue examines what happens to discarded furniture treated with problem flame retardants, and the implications of a new, genetically diverse mouse model.

Inside the Institute

NIEHS scientists reflect on the legacy of Tuskegee during Black History Month Video

This February, graduates of the Tuskegee University School of Veterinary Medicine paused to share memories of their alma mater during Black History Month at NIEHS.

Science Notebook

Systems biology pioneer Leroy Hood to give Rodbell Lecture Video

Founder of the Institute for Systems Biology, Hood will lecture on systems medicine and proactive personalized medicine.

RTI announces upcoming metabolomics opportunities

In an invitation to scientists at NIEHS, the metabolomics research center at RTI announced its spring meeting and an upcoming international conference.

Extramural Research

Extramural papers of the month

- Prenatal BPA exposure linked with higher levels of oxidative damage
- Vitamin B protects against DDT-associated fertility problems
- BPA may be especially harmful to heart health of females
- People and mice share epigenetic differences tied to obesity

Intramural Research

Intramural papers of the month

- NTP finds that indium-induced pulmonary toxicity depends on particle solubilization
- Ctp1 acts as a bridge over troubled DNA
- Genome-wide p53 binding is independent of chromatin state, but response depends on it
- The role of the NLRP3 inflammasome in obesity resistance and insulin sensitivity of NAG-1 mice
- Testosterone and peritubular myoid cells involved in maintenance of spermatogonial stem cell microenvironment

Calendar of Upcoming Events

- **March 2-3**, in Rodbell Auditorium, March 2, 8:30 a.m. – 6:00 p.m., March 3, 8:30 a.m. – 4:00 p.m. — Institute of Medicine Roundtable on The Interplay Between Environmental Exposures and Obesity, register
- **March 3**, in the Executive Conference Room, noon – 1:00 p.m. — Receptor Mechanisms Discussion Group Seminar Series, with Richard Woychik, Ph.D., discussing "Role of Repetitive Elements in Mediating Environmental Changes in Gene Expression"
- **March 5-6 (Off-site event)**, at the NIH Natcher Conference Center in Bethesda, Maryland, 8:30 a.m. – 5:00 p.m. — International Symposium on Alternatives Assessment: Advancing Science and Practice, with panelist Linda Birnbaum, Ph.D.
- **March 5-8 (Off-site event)**, at the San Diego Convention Center, California — ENDO 2015
- **March 10**, in Rodbell Auditorium, 11:00 a.m. – noon — Dr. Martin Rodbell Lecture Series Seminar by Leroy Hood, M.D., Ph.D., exploring "Systems Medicine and Proactive P4 Medicine: Catalyzing a Revolution in Healthcare"
- **March 10**, in Rodbell Auditorium, 1:30 – 2:30 p.m. — 2015 Spirit Lecture, featuring Hannah Valantine, M.D., discussing "Lessons Learned From My Career Path: Science to Diversity"
- **March 12 (Off-site event)**, at the North Carolina Biotechnology Center in Research Triangle Park, North Carolina, 3:30 – 7:00 p.m. — 2015 Exchanging Ideas Summit: Game Changing Science, with Richard Woychik, Ph.D., giving keynote address, register
- **March 14**, in Rodbell Auditorium, 8:00 a.m. – 2:00 p.m. — Triangle Consortium for Reproductive Biology 2015 Symposium
- **March 16**, in Rodbell Auditorium, 11:00 a.m. – 5:00 p.m. — National Advisory Environmental Health Sciences Council meeting, webcast
- **March 17**, in Rodbell Auditorium, 3:00 – 4:00 p.m. — 2015 Wetterhahn Award seminar by Corin Hammond, Ph.D.
- **March 18-19**, in Rodbell Auditorium, 8:00 a.m. – 5:00 p.m. — Workshop on population-based mouse resources
- **March 26 (Off-site event)**, at the North Carolina Museum of Natural Sciences in Raleigh, North Carolina, 9:00 a.m. – 5:00 p.m. — NC BREATHE Conference on Bridging Research on Economics, Air Quality, and The Health of Everyone, featuring grantee Michelle Bell, Ph.D.
- View More Events: NIEHS Public Calendar

NIEHS Spotlight

NIEHS highlights public health and disaster research at oil spill conference

By Joe Balintfy

Researchers from more than 35 states and 20 countries met Feb. 16-19 in Houston to focus on results from oil spill, ecosystem, and public health research, five years after the Deepwater Horizon disaster. The 2015 Gulf of Mexico Oil Spill and Ecosystem Science Conference attracted representatives from 140 universities, 80 companies, and 17 government agencies. Altogether, about 1,000 people participated in sharing the results of research and application of findings.

"This year's meeting highlighted the opportunity we have to do more, and to increase attention to the importance of health research related to the Gulf oil spill," said NIEHS and National Toxicology Program Director Linda Birnbaum, Ph.D.

In her keynote presentation during the session on human health, Birnbaum reviewed National Institutes of Health (NIH) and NIEHS accomplishments, including new health and safety resilience training, ongoing efforts of the GuLF STUDY, toxicology research, and the Deepwater Horizon Research Consortia, which created community-university partnerships aimed at addressing the health effects stemming from the oil spill. Highlighting the importance of community involvement, Birnbaum said, "Communities know who they are, know what concerns them, and want to work with researchers to be part of the program."

"You can't do environmental health research unless you get the communities involved," Birnbaum said at the conference. (Photo courtesy of Joe Balintfy)

Other NIEHS grantees presenting at the conference

Emily Harville, Ph.D., Tulane University — "Experience of the Deepwater Horizon Oil Spill and Mental Health in Pregnant and Reproductive-aged Women"

Jessi Howard, Tulane University — "Community-based Participatory Research in Southeast Louisiana on Challenges in Determining Air and Foodborne Exposures in Low-income Participants"

Arti Shankar, Ph.D., Tulane University — "Quality of Life as a Measure of Resilience in Gulf Coast Women Pregnant for the First Time"

Mark Wilson, Ph.D., Tulane University — "A Targeted Risk Assessment of Polycyclic Aromatic Hydrocarbon Exposure in Vietnamese-American Shrimp Consumers Following the Deepwater Horizon Oil Spill"

She also emphasized the need to leverage the research platforms and relationships that have developed. In particular, the new NIEHS Disaster Research Response Project is addressing challenges in carrying out timely health research in response to future disasters and emerging threats (see text box).

Richard Kwok, Ph.D., left, co-study leader on the NIEHS GuLF STUDY, talks with Miller, right, who presented "Translating Lessons From the Gulf Oil Spill Into Improved Disaster Health Research." (Photo courtesy of Joe Balintfy)

Gaps to gains

Organized by the Gulf of Mexico Research Initiative (GoMRI), the conference included more than 500 oral and poster presentations. One session, titled Gaps to Gains, held particular interest for NIEHS staff and grantees, as it addressed two important conference themes — public health and community engagement. NIEHS presenters for this session included Birnbaum; Dale Sandler, Ph.D.; Christine Ekenga, Ph.D.; Aubrey Miller, M.D.; Joseph (Chip) Hughes, and predoctoral fellow Kaitlyn Gam.

Sandler, Ekenga, and Gam shared findings from the GuLF STUDY. Sandler pointed out that participants in the study reported cough, shortness of breath, wheeze, and tightness in the chest. "Workers had a small but statistically significant higher prevalence of all four of the respiratory symptoms at the time they enrolled in the study, after we took into account where they lived and the other potential confounding factors," Sandler said.

Miller and Hughes shared presentations on new efforts to perform timely disaster health research, and build responder mental health resilience. "Continued NIEHS involvement with GoMRI and the Deepwater Horizon oil spill will help assure that human health and environmental health impacts are not forgotten or overlooked as the Gulf recovers," said Hughes.

Some of the NIEHS participants and presenters gathered at the NIEHS display were, from left, Balintfy; Hughes; April Bennett; Gam; Ekenga; Sandler; Kwok; and Miller. (Photo courtesy of NIEHS)

Grantee perspectives

Several NIEHS grantees also presented during the Gaps to Gains session, many from Tulane University (see sidebar). Stacy Drury, M.D., Ph.D., associate professor of psychiatry and behavioral sciences at Tulane, discussed chemical and nonchemical stressors linked with the spill, and the impact on telomere length, which is an indicator of stress and health, in infants and young children. She said that mothers, through their parenting, may be able to counter the biological effect of stressors.

Other speakers discussed mental health, ways to quantify health impacts, and community-based participatory research related to the Gulf oil spill. "The university-community partnerships are collaborating on approaches and sharing results, to understand better the interplay and effects of multiple stressors on human health," said Birnbaum.

Disaster research exercise prepares local, national participants

Prior to the conference, more than 140 participants, including police, firefighters, representatives from state and local health departments, academics, and government representatives, met for the second tabletop exercise organized by the NIH Disaster Research Response Project. NIEHS and partners reviewed the realistic but fictitious scenario of a Category 4 hurricane hitting Galveston Island and sending a 20-foot storm surge up the Houston ship channel, which is lined with oil tankers, refineries, and neighborhoods.

Progress in disaster preparedness, response, and recovery may be hampered by the absence of scientific data to guide procedures, citizen action, and the use of medical countermeasures. "Short and long-term health consequences from a variety of exposures often go unknown," said Hughes. "Researchers have identified behavioral health consequences, but don't yet fully understand the needed preventive and mitigating measures. While there are many reasons for the overall lack of disaster science, a major contributor is the inability to conduct disaster research in the immediate post-disaster period, when critical information is most perishable."

The experts discussed oil spills from tankers and refineries, as well as likely fires. Responders would have to prepare for air and water pollution problems, as well as flooding that would affect a large number of people.

"What we realized is that this storm surge would cause flooding for miles," said Birnbaum. "And that 1.5 million residents would be displaced from the area."

Participants exchanged ideas about what they would need to do and learned the importance of doing research in a scenario like this. "Disaster health research helps us understand ways to prevent adverse impacts in the future," said Birnbaum.

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

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Sandler honored by AMA for outstanding government service

By Eddy Ball

Dale Sandler, Ph.D., head of the NIEHS Epidemiology Branch, is the recipient of a Dr. Nathan Davis Award for Outstanding Government Service, a top honor named for the founding father of the American Medical Association (AMA).

Sandler and six other winners received their awards at the Nathan Davis Awards reception and dinner that concluded the AMA National Advocacy Conference Feb. 23-25 at the Grand Hyatt in Washington, D.C.

The award specifically recognizes Sandler for her pioneering contributions to the study of chronic disease.

"With this award, Dale joins an elite group of past winners, who have included senators, representatives, surgeons general, and federal executives recognized for their public service above and beyond the call of duty," said Linda Birnbaum, Ph.D, NIEHS and National Toxicology Program director. "It is a great honor and one which Dale richly deserves for her selfless efforts to improve public health."

Highlighting Sandler's leadership of the Sister Study and GuLF STUDY

"Dr. Sandler's trailblazing work in the field of research, through projects like the Sister Study and GuLF STUDY, have shed light on the role that environmental and lifestyle factors play in disease," said Barbara McAneny, M.D., AMA chair.

"Her innovative vision has led to a greater understanding of risk factors for disease and the improvement of public health," continued McAneny. "Her research on the health of oil spill cleanup workers through the GuLF STUDY represents a unique response to an emerging environmental and public health disaster."

The award recognizes elected and career officials in federal, state, or municipal service whose outstanding contributions have promoted the art and science of medicine and the betterment of public health. During the past 26 years, the AMA has honored more than 200 men and women with the Dr. Nathan Davis Award.

In addition to the studies singled out by the AMA, Sandler is a lead researcher for the large-scale Agricultural Health Study. She and members of her Chronic Disease Epidemiology Group lead several additional stand-alone, add-on, and nested studies. (Photo courtesy of Steve McCaw)

Sandler's award is the latest in a long list of honors Sandler has received for her work in epidemiology and public health. She was elected as a fellow of the American College of Epidemiology, a member of the American Epidemiological Society, and an alumni member of the Alpha Chapter of the Delta Omega Public Health Honor Society at the Johns Hopkins Bloomberg School of Public Health. In addition, the American College of Epidemiology presented her with its Leadership and Distinguished Service Award and its Leadership Recognition. In 2010, she received the U.S. Environmental Protection Agency Office of Research and Development Honor Award, a Bronze Medal team award.

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Assessing alternatives to substances that present exposure risk

By Kelly Lenox

When faced with evidence that environmental exposure to a certain substance can harm public health, decision makers typically concentrate on determining safe levels. They should also begin evaluating alternatives to these substances, said Joel Tickner, Sc.D., during his Feb. 3 talk at NIEHS, "Building a Research Agenda and Scientific Community of Practice for Chemical Alternatives Assessment."

Alternatives assessment refers to analyzing candidate substances to determine whether they are truly safer than those they are meant to replace. Tickner is an associate professor of community health and sustainability at the University of Massachusetts Lowell. The university, along with NIEHS and EPA, is sponsoring an international symposium on alternatives assessment March 5-6 (see sidebar).

"I've always really liked his approach, which is to focus on the solutions and what we need to get there, rather than focusing on the problems," said Linda Birnbaum, Ph.D., director of NIEHS and the National Toxicology Program, who hosted the talk.

Guidance for evaluations

The shift to focusing on solutions favors innovation rather than setting limits, said Tickner. Market forces now encourage retailers and manufacturers to search for safer alternatives, which drives the need for evaluation tools (see text box). "The goal is to use a considered process of alternatives evaluation so we avoid jumping out of the frying pan into the fire, as we have seen with bisphenol A [BPA] alternatives," he said, referring to indications that BPA alternatives may also present health concerns.

Tickner highlighted a framework developed by the National Research Council (NRC) of The National Academies. In addition to exposure hazards, the framework considers the life cycle of a substance or product, the performance of alternatives, and economic factors. "We need a flexible, adaptable approach to alternatives assessment that doesn't lock people into a specific way of doing things, but ensures a comprehensive look at the process, minimizes unintended consequences, and supports informed transition," he explained.

International Symposium on Alternatives Assessment — Advancing Science and Practice

March 5-6, 2015
National Institutes of Health, Bethesda, Maryland
Free, registration required

The Lowell Center for Sustainable Production at the University of Massachusetts Lowell, in conjunction with NIEHS, and with financial sponsorship from the U.S. Environmental Protection Agency and ToxServices, have organized the symposium to build up the scientific field and create a community of practice. Birnbaum will give a keynote address.

Data gaps call for novel approaches

A National Academy of Sciences panel analyzed the literature on alternatives assessment and developed a framework to support assessment processes. Tickner and two colleagues from the Academy team published their conclusions in a Jan. 27 editorial in Environmental Science and Technology.

Important differences in approaches to handling data gaps led the editorial authors to call for increased use of novel data streams. For example, high throughput screening and computer models and simulations can help ensure that alternatives assessment is not sidetracked by lack of data, they said.

Research agenda

Tickner kept his talk focused on the practical. "How do we pull together all the data so there is information decision makers can act on?" he asked. By way of an answer, Tickner outlined an agenda for future research.

- Develop more core hazard data for key health endpoints.
- Work toward data-type integration and filling of data gaps, for efficient review of more chemicals.
- Improve tools for analyzing exposure tradeoffs.

Tickner stressed that when an organization identifies a chemical as problematic, they should look at alternatives to avoid regrettable substitutions. (Photo courtesy of Steve McCaw)

- Develop tools that incorporate life cycle thinking, for example, manufacturing and use, byproducts, and end products.
- Create tools for integrating all these attributes into the decision-making process.

In closing, Tickner emphasized the need to incorporate what he called alternative thinking into all scientific endeavors, particularly in the fields of toxicology, ecological toxicology, and risk assessment. It is important to examine health threats, as well as evaluate what approaches are safer.

Mark Miller, Ph.D., left, Birnbaum's chief of staff, listens along with Andy Rooney, Ph.D., deputy director of the NTP Office of Health Assessment and Translation. In response to Rooney's question about the timing of life cycle analysis, Tickner suggested one might look at toxicity first and then complete a life cycle analysis on substances that appear safer, if needed, to distinguish between using alternatives or reducing impacts. (Photo courtesy of Steve McCaw)

As a data scientist in the NIEHS Office of Scientific Information Management, Becky Boyles is a key member of the NIEHS Data Science Interest Group, which formed in late 2014. (Photo courtesy of Steve McCaw)

Citation: Tickner JA, Dorman DC, Shelton-Davenport M. 2015. Answering the Call for Improved Chemical Alternatives Assessments (CAA). Environ Sci Technol 49(4):1995-1996.

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Resources

Listed below are some of the alternatives assessment approaches and resources Tickner shared.

- A Framework to Guide Selection of Chemical Alternatives — NRC comprehensive approach to alternatives assessment that addresses the life cycle of a substance or product, performance of alternatives, and economic factors.
- Organisation for Economic Co-operation and Development Substitution and Alternatives Assessment Toolbox — one-stop shop for alternatives assessment tools.
- GreenScreen For Safer Chemicals — publicly available and transparent chemical hazard screening method to help move toward the use of safer chemicals.
- Commons Principles for Alternatives Assessment — Chemical commons group principles to guide alternatives assessments when making substitutions for hazardous products.
- Occupational Safety and Health Administration toolkit — framework to help small and medium size businesses transition to safer chemicals.
- Interstate Chemicals Clearinghouse — guide to a multistep framework for evaluating alternatives.
- European Chemicals Agency REACH — authorization procedure for substances of very high concern establishes procedures for alternatives assessment for continued use of such substances.
- California Safer Consumer Products program — requires alternatives assessment report for manufacturers and others.

NIEHS funds six early-career researchers for innovative science

By Christine Bruske Flowers

New grants totaling $3 million will go to six outstanding early-career scientists, bridging a funding gap to independent biomedical research. NIEHS created the highly competitive grant, known as the Outstanding New Environmental Scientist (ONES) award, in 2006 to encourage early stage researchers who want to discover how our environment influences human health.

The award is notable for funding emerging scientists, typically in their mid-30s. More often, scientists are awarded their first research grant around age 42.

"The ONES funding comes at a critical time in a research career when someone is trying to set up their own lab to pursue their unique ideas," said Linda Birnbaum, Ph.D., NIEHS and National Toxicology Program director. "These early-career scientists are so innovative, and they inspire the entire research community. I believe this program will spur new biomedical research and lead to important medical breakthroughs."

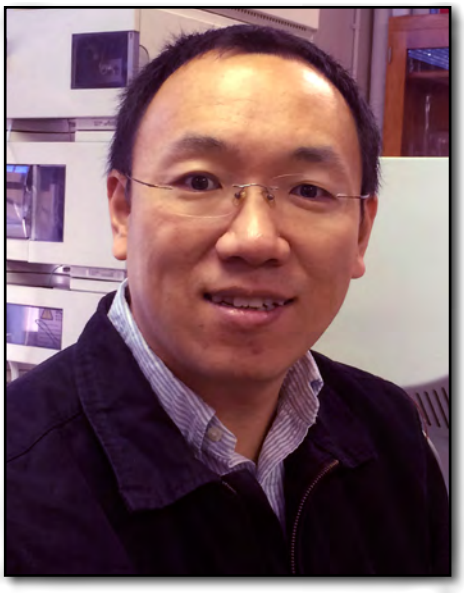
The 2015 ONES awardees will study connections between environmental exposures to arsenic, ozone, and other substances, and health problems, including cognitive function, asthma, and DNA damage.

"This talented group of awardees shows tremendous promise," said Gwen Collman, Ph.D., who oversees all NIEHS grants as director of the Division of Extramural Research and Training. "We believe the ONES grant will provide a firm foundation for building a successful career."

Neel Aluru, Ph.D., at Woods Hole Oceanographic Institution in Massachusetts, will use zebrafish models to study how early-life exposures to toxic chemicals may lead to developmental disabilities. (Photo courtesy of Neel Aluru)

Kara Bernstein, Ph.D., at the University of Pittsburgh, will study how errors in DNA repair lead to tumor growth, and how at-risk individuals may be more sensitive to DNA damage. (Photo courtesy of Joshua Franzos)

Samir Kelada, Ph.D., at the University of North Carolina at Chapel Hill, will use innovative approaches to identify genes and pathways that play a role in the effect of ozone on asthma. (Photo courtesy of Samir Kelada)



Kun Lu, Ph.D., at the University of Georgia, will study the interaction between the gut microbiome and arsenic, a widespread environmental pollutant and known human carcinogen. (Photo courtesy University of Georgia)

William Mack, M.D., at the University of Southern California, will research how particulate matter exposure can be toxic to blood vessels in the brain, and identify risks to cognitive health in vulnerable populations. (Photo courtesy of William Mack)

Dana Miller, Ph.D., at the University of Washington, will explore the long-term effects of toxic substances on basic physiology. (Photo courtesy of BethAnn McLaughlin)

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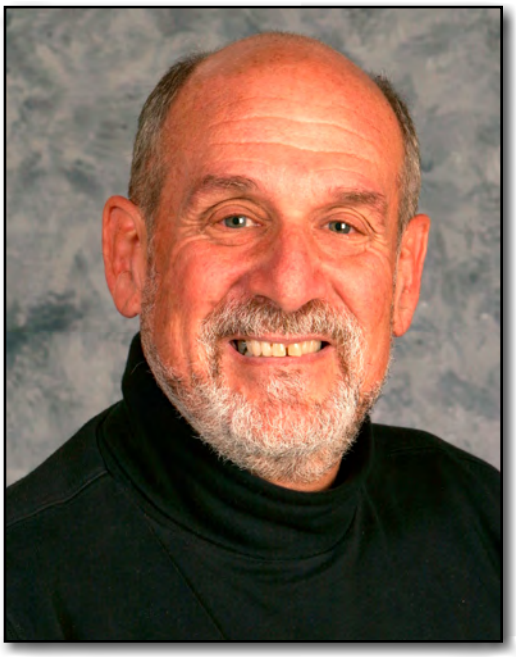
Miller receives Target ALS award to study therapy for Lou Gehrig's disease

By Eddy Ball

In January, NIEHS lead investigator David Miller, Ph.D., received a 3-year grant to improve therapeutic drug delivery for treating amyotrophic lateral sclerosis (ALS), the fatal neurodegenerative condition also known as Lou Gehrig's disease.

The grant from Target ALS will provide Miller with $138,770 to support research into how the central nervous system (CNS) becomes drug resistant during the progression of ALS. He and his group will also work to create a strategy for delivering therapeutic drugs to where they need to be, across the blood-brain and blood-spinal cord barriers that protect the CNS from environmental and other potentially damaging exposures.



"Basically, we hope to be able to stop the disease-driven and selective tightening of the brain's barriers to certain drugs," he explained. "Doing this may improve therapy with current and novel therapeutics." (Photo courtesy of Steve McCaw)

"This is a wonderful opportunity for our group to translate our years of research into regulation of chemical transport across the tissue barriers that protect the CNS, to improve treatment for this terrible disease," said Miller. "As we've learned, the body doesn't discriminate very well between harmful chemicals and therapeutic drugs, and this protective mechanism contributes to the poor success rate of CNS drug candidates."

Experiments will focus initially on enhancing the effectiveness of riluzole, the only drug currently approved by the U.S. Food and Drug Administration for treatment of ALS. Because of the tissue barriers to delivery, riluzole typically prolongs survival by only around 2 months, about as long as it took for the ALS Association Ice Bucket Challenge to go viral last summer.

Pasinelli and Trotti established the Weinberg Unit in 2006 as part of their long-time collaboration on ALS and pharmacoresistance. Pasinelli, Trotti, and Miller have co-authored two studies, including a 2014 review published in Brain Research. (Photo courtesy of Thomas Jefferson University)

Breaking down silos in ALS research and fostering collaborations

Established in 2013, Target ALS is promoting a systemized approach to screening ALS therapies and generating a pipeline of candidate therapeutic targets for drug development. Its goal is to provide a central organization for scientists, academics, and health care and business professionals to share ideas, progress, and discoveries.

Miller will be part of consortium that includes neurobiologists Piera Pasinelli, Ph.D., and Davide Trotti, Ph.D., founding co-directors of the Thomas Jefferson University Weinberg Unit for ALS Research in Philadelphia. The team will advance previous work on transport proteins, which function as drug efflux pumps within the tissue barriers and serve as selective gatekeepers for the central nervous system.

The aims of Miller's part of the project are to use a mouse model of ALS to determine the critical period during disease progression when transporter activity and expression increases; map the signals within the neurovascular unit responsible for those increases; and devise a strategy to block signaling, prevent transporter upregulation, and increase delivery of riluzole and other therapeutics to the CNS.

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Environmental exposure research and public policy

By Deepa Singh

In addition to providing data on the health effects of exposures to harmful chemicals, researchers can help promote policies to reduce or prevent exposures, said Tracey Woodruff, Ph.D., during her Feb. 2 NIEHS Keystone Science Lecture Seminar Series talk. A professor at the University of California, San Francisco School of Medicine, Woodruff studies how exposures affect early human development.

Opening with the success story of phasing out lead from gasoline and paint, Woodruff pointed out that the neurotoxic effects of lead were well known even before Benjamin Franklin wrote about lead in his famous 1786 letter to Benjamin Vaughan. Although earlier identification of risk can improve public health, lead is only one contaminant of concern. "While the production of lead was going down, the production of manufactured chemicals used in many everyday products was going up," she said.

According to Woodruff, 9.5 trillion pounds of chemicals were produced in 2012, or approximately 30,000 pounds per person in the U.S. However, little is known about the uses and health effects of these chemicals. "Understanding the relationship between exposures and health effects, particularly during the developmental periods, is important to prevent harm," she said.

Scanning for chemicals in biological samples

Woodruff also addressed the importance of studying mixtures of chemicals. "We wanted to know the status of combined environmental exposures, because early pregnancy is a vulnerable period of development," she said. In a study using data from the ongoing National Health and Nutrition Examination Survey (NHANES), a program of studies designed to assess the health and nutritional status of adults and children in the United States, Woodruff and colleagues found 43 different industrial chemicals in more than 99 percent of the pregnant women who participated.

There are challenges to scanning biological samples for multiple chemicals, Woodruff noted. One newer method, known as time-of-flight mass spectrometry, enables unbiased detection, or discovery of molecules that were not targeted for analysis.

In a recent study, Woodruff and colleagues analyzed blood samples from 80 pregnant women. They found potential chemical hits for phthalates, pesticides, and phenols in numbers much higher than the 43 chemicals previously reported. NHANES testing addressed only 11 percent of the chemicals identified in these women. "There are lots of chemicals that are measured in almost everyone, and looking at these exposure profiles will help us understand the influence on health outcomes," she said.

Woodruff, an NIEHS grantee, directs the program on reproductive health and the environment and is a professor in the department of obstetrics, gynecology, and reproductive sciences at the University of California, San Francisco. (Photo courtesy of Steve McCaw)

Reducing the gap

"Our goal is to shrink the time between when we have a scientific discovery and when we take an action to limit exposures," Woodruff continued. "We want to make the science more useful for public health decisions."

For example, phthalates, which are present in personal care products, were not originally part of NHANES measurements, she said. When the Centers for Disease Control and Prevention initiated a larger scale biomonitoring program in 2000, they measured phthalates across the whole U.S. population. Notably, the highest levels were found in women of reproductive age.

Woodruff's talk prompted lively discussion from the audience, including Sue Fenton, Ph.D., left, head of the National Toxicology Program (NTP) Reproductive Endocrinology Group, and Alfonso Latoni, Ph.D., head of the Division of Extramural Research and Training Scientific Review Branch. (Photo courtesy of Steve McCaw)

Since then, use of certain phthalates has decreased. "There was a response in the marketplace because of these data, where an exposure and its source were identified, and then the legislative and nongovernmental groups took action," Woodruff said. Legislation and market pressure to remove phthalates from beauty products and toys has resulted in lower levels detected in more recent NHANES samples, she said.

Woodruff closed her talk on an optimistic note, saying that physicians have become key partners, by informing not only their patients, but also policymakers in Washington, D.C., about the impact of environmental chemicals on the public's health.

Citation: Woodruff TJ, Zota AR, Schwartz JM. 2011. Environmental chemicals in pregnant women in the United States: NHANES 2003-2004. Environ Health Perspect. 19 119(6):878-885.

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

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

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Woodruff spoke to a room full of NIEHS and NTP scientists. The talk was hosted by Kimberly Gray, Ph.D., who directs the NIEHS and Environmental Protection Agency Centers for Children's Environmental Health and Disease Prevention Research. (Photo courtesy of Steve McCaw)

New RESTORE Act center builds on NIEHS experience

By Joe Balintfy

Two NIEHS Environmental Health Sciences Core Center leaders are part of a new research consortium, announced Jan. 16, that is dedicated to successfully restoring and sustaining a healthy environment for humans and animals in the Gulf of Mexico region. The Texas OneGulf Center of Excellence is one of three new Centers of Excellence in Research established under the 2012 Resources and Ecosystems Sustainability, Tourist Opportunities, and Revived Economies of the Gulf Coast States (RESTORE) Act.

Grantees Cheryl Walker, Ph.D., and Cornelis (Kees) Elferink, Ph.D., helped establish Texas OneGulf Consortium. Walker heads the Center for Translational Environmental Health Research at the Texas A&M Health Science Center, (see story). Elferink leads the Center in Environmental Toxicology (CET) at the University of Texas Medical Branch at Galveston.

"Having two NIEHS Centers in Texas allowed Drs. Walker and Elferink to bring both expertise and infrastructure to the human health component of the new RESTORE Act center," said Claudia Thompson, Ph.D., program lead for the NIEHS Environmental Health Sciences Core Centers and head of the NIEHS Population Health Branch. "Because of their experience as NIEHS center

"We are delighted that both of the NIEHS centers in the Gulf region will be contributing to Texas OneGulf efforts," said Walker. (Photo courtesy of Cheryl Walker)

directors, they had immediate access to resources and capacity, such as clinics, communications and outreach capabilities, and connections to the community."

RESTORE Act

The RESTORE Act directs a portion of the penalties paid by those responsible for the 2010 Deepwater Horizon oil spill into a trust fund to support Gulf Coast restoration. The act directs that a portion of the trust fund be used to establish centers of excellence in the five Gulf states affected by the spill. At this time, roughly $20 million is available for each of those states to establish one or more centers.

Each RESTORE Act Center of Excellence will focus on science, technology, and monitoring. Center goals include ecosystem research, mapping of the Gulf of Mexico, and strategies to support safe and sustainable living. Three centers have been established so far — Texas OneGulf; Subsea Systems Institute, also in Texas; and the Water Institute of the Gulf in Louisiana.

Texas OneGulf

The Texas OneGulf Consortium will study sustainability, restoration, and protection of the coast and deltas. Led by Harte Research Institute for Gulf of Mexico Studies at Texas A&M University-Corpus Christi, the consortium includes eight other institutions (see text box).

Walker will serve as deputy director of Texas OneGulf, and Elferink will lead the human health and wellness component. One of the first activities launched by the new center will be a disaster research response project, which Sharon Croisant, Ph.D., director of the Community Outreach and Engagement Core for CET, was instrumental in designing.

"Kees and I have a long-standing working relationship that enabled us to rapidly mobilize both our centers to capture this opportunity, providing a unique human health and wellness focus for OneGulf lacking in the other RESTORE Act centers," said Walker. "This opportunity will complement ongoing human health research directed by Kees and supported through the NIEHS Deepwater Horizon Research Consortia."

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

As director of the Center in Environmental Toxicology, Elferink oversees research focusing on asthma pathogenesis, environmentally linked carcinogenesis, and disease states induced by reactive oxygen stress. (Photo courtesy of Cornelis Elferink)

Thompson oversees NIEHS funding for 20 centers across the country that share scientific equipment, facilities, and other resources among researchers tackling related environmental health questions. (Photo courtesy of Steve McCaw)

Texas OneGulf Center of Excellence partners

- Harte Research Institute for Gulf of Mexico Studies at Texas A&M University-Corpus Christi
- Biological and Environmental Sciences at the University of Texas at Brownsville
- Center for Translational Environmental Health Research
- Center for U.S. and Mexican Law at the University of Houston Law Center
- Geochemical and Environmental Research Group and Department of Oceanography at Texas A&M University
- Gulf of Mexico Coastal Ocean Observing System Regional Association
- Marine Biology, Science, and Engineering departments at Texas A&M University at Galveston
- Sealy Center for Environmental Health and Medicine at the University of Texas Medical Branch
- The Meadows Center for Water and the Environment at Texas State University

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Linking high-throughput data to human exposures

By Catherine Sprankle

NIEHS scientists and colleagues throughout the world are evaluating the use of high-throughput methods to identify chemicals that could cause human illness. Once such chemicals are identified, a process known as *in vitro* to *in vivo* extrapolation links the high-throughput data to human doses. The process takes into account metabolic differences between cell-based systems and whole organisms.

In a Jan. 27 webinar, organized by the NTP Interagency Center for the Evaluation of Alternative Methods (NICEATM; see sidebar), more than 250 viewers from around the world learned about *in vitro* to *in vivo* extrapolation from two experts.

The webinar featured presentations by John Wambaugh, Ph.D., physical scientist in the National Center for Computational Toxicology at the U.S. Environmental Protection Agency (EPA), and Barbara Wetmore, Ph.D., senior research investigator at the Hamner Institutes for Health Sciences. Organized on behalf of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), it was the first in a series of Communities of Practice webinars that will provide in-depth examinations of topics related to chemical screening and safety testing.

Wambaugh used mathematical models and computer simulations to predict doses that would result from chemical exposure in humans. (Photo courtesy of Keith Tarpley)

Building on ToxCast data

EPA scientist Anna Lowit, Ph.D., co-chair of ICCVAM, introduced the speakers. “This is a very exciting time in risk assessment and toxicology,” she said. Lowit emphasized the key role that *in vitro* to *in vivo* extrapolation plays in applying high-throughput screening data to human risk assessment.

Wambaugh described both the lab work and the computations required to link high-throughput screening data to human doses of concern. According to Wambaugh, two factors complicate the process of making that link — diversity in human sensitivity and variations in chemical properties that result in some chemicals being retained by the body longer than others. Wambaugh described ongoing studies by EPA and collaborators to generate human metabolism data. "These data will eventually allow determination of human oral equivalent doses for most ToxCast chemicals," he said.

ToxCast is a multiyear effort launched by EPA in 2007 that uses high-throughput screening to expose living cells or isolated proteins to chemicals. The cells or proteins are then screened for changes in biological activity that may suggest potential toxic effects.

Wetmore described experiments that measured the effects of specific metabolic enzymes on a group of chemicals. (Photo courtesy of The Hamner Institutes for Health Sciences)

Examining the effects of human diversity

Wetmore discussed the effects of human diversity. "Relying on data for a generic population could lead us to seriously underestimate the risk to a susceptible subpopulation," she said. Wetmore described *in vitro* to *in vivo* extrapolation studies that accounted for human variation and produced predictions of how the body's handling of chemicals might differ in healthy people compared to ill people, adults compared to children, and in people with different genetic backgrounds.

These studies predicted populations that might be most susceptible to toxicity from a particular chemical. For example, when comparing populations with similar external exposures to the insecticide carbaryl, newborns were predicted to have higher blood levels of the substance than other populations. For the fungicide difenoconozole, people with kidney disease were predicted to have higher blood levels.

Several webinar viewers asked questions of each of the speakers. In his closing remarks, NICEATM Director Warren Casey, Ph.D., noted the strong interest in the webinar and shared that NICEATM would explore organizing a workshop on this topic.

Finding alternatives to animal testing

The term alternative methods refers to methods of research and testing that use fewer or no animals, or that reduce animal pain and distress. Congress established several groups to ensure the involvement of all stakeholders in development of such methods.

- The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) coordinates the activities of member federal agencies to replace, reduce, or refine animal use.
- The NTP Interagency Center for the Evaluation of Alternative Methods (NICEATM) is an office within the National Toxicology Program (NTP) that supports ICCVAM activities and NTP projects. The center is involved with development of novel approaches to testing.

NICEATM supports international efforts to develop new test methods

NICEATM scientists joined international collaborators at meetings in Kyoto, Japan, to assess the progress of other efforts to develop nonanimal methods for chemical safety testing.

- Nicole Kleinstreuer, Ph.D., a NICEATM support contractor, participated in meetings Jan 29-31 of the validation study management team. The validation studies are designed to determine the usefulness and limitations of methods that use collagen membranes to identify potential eye irritants and skin sensitizers. Experimental work on the eye irritation study is complete and the method will be submitted for international approval later this year. Experimental work on the skin sensitization study will be completed later this spring.

- Casey participated in two study management team meetings in mid-February to review results from ongoing validation studies of new test methods. One method uses cultured corneal cells to identify eye irritants. The other uses embryonic stem cells to identify potential developmental toxicants.

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

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NIEHS fellow to receive achievement award at upcoming SOT conference

By Kelly Lenox

The Society of Toxicology announced in late January that NIEHS postdoctoral fellow Erin Quist, D.V.M., was this year's recipient of the Roger O. McClellan Student Award. Quist is an Intramural Research and Training Award fellow in the National Toxicology Program (NTP) Reproductive Endocrinology Group, led by Sue Fenton, Ph.D., and the NTP Pathology Group headed by David Malarkey, D.V.M., Ph.D.

"Erin is an incredibly hard worker, and very deserving of this recognition," Fenton said. "The depth of experience she brings to this lab has really enhanced our work."

Quist is a Ph.D. candidate at North Carolina State University College of Veterinary Medicine, studying comparative pathology. She earned her D.V.M. from Colorado State University and completed a three-year residency at Texas A&M University in anatomic veterinary pathology before joining NTP in 2011.

Roger and Kathleen McClellan established the award to encourage individuals with a D.V.M. degree to pursue careers in biomedical research, including comparative toxicology and pathology.

"I am extremely honored to receive this award and am very grateful to the Toxicologic and Exploratory Pathology and the Comparative and Veterinary Specialty Sections of the SOT for selecting me as this year's recipient." Quist said. (Photo courtesy of Steve McCaw)

The award is based on the scientific merit of research proposed for presentation at the Society of Toxicology (SOT) annual meeting (see text box). Special consideration is given to research abstracts that exemplify the role of comparative medicine in evaluating the effects of exposure to chemicals or physical agents.

"It's wonderful to receive recognition indicating that my work has the potential to significantly impact the scientific community," Quist said. "[It also] represents the effectiveness of the NTP training program, as well as my commitment to the fields of comparative and toxicologic pathology."

Fenton's group focuses on the developmental impacts of numerous environmental chemicals. (Photo courtesy of Steve McCaw)

PFOA and liver toxicity

Her award-winning abstract is titled "Hepatic mitochondrial alteration in CD-1 mice associated with prenatal exposures to low doses of perfluorooctanoic acid (PFOA)." Quist and her colleagues found increased numbers of mitochondria, the power plant of cells, and alterations in their function in the liver tissue of PFOA-exposed mice. They are conducting further studies to determine the precise mode of action involved in PFOA-induced liver injury.

PFOA is used in the manufacture of fluoropolymers, which have thousands of important manufacturing uses. The U.S. Environmental Protection Agency nominated PFOA for NTP study in 2003. Since then, NTP scientists and contractors have performed short-term toxicity, long-term carcinogenicity, and other studies on the compound.

Society of Toxicology meets March 22-26 in San Diego

By Robin Mackar

About 6,500 toxicologists representing 50 countries will participate in the 54th annual meeting of the Society of Toxicology. Scientists from NIEHS and NTP will be involved in workshops, poster sessions, symposia, and other activities featuring a broad range of advances in toxicological science (see highlights below).

The meeting offers something for everyone, from the annual awards ceremony on Sunday evening, to the opening plenary session Monday morning featuring one of the world leaders in genomics research, Craig Venter, Ph.D., founder, chairman, and CEO of the J. Craig Venter Institute.

Monday, March 23, 1:30 p.m. — The Meet the Directors session is always popular at SOT. This year's session features Linda Birnbaum, Ph.D., director of NIEHS and NTP, and Jim Jones, assistant administrator of the U.S. Environmental Protection Agency Office of Chemical Safety and Pollution Prevention. The informal event lets attendees ask the two government leaders questions about scientific directions, priorities, training opportunities, and more.

Tuesday-Wednesday, March 24-25, 9:30 a.m. – 4:30 p.m. — Another popular event is the Research Funding Information Room, staffed by NIEHS Division of Extramural and Research Training (DERT) staff. Attendees, especially new researchers, can stop by for one-on-one conversations about scientific review or grant opportunities.

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Monday, March 23, noon — A brown bag luncheon with DERT staff will be held on strategies for submitting successful grant applications.

Thursday, March 26, 9:00 – 11:45 a.m. — The Comprehensive Analysis of Nano Silver Toxicity Profiles: Known, Unknown, and Surprises session, led by DERT staff, will provide updates from NIEHS grantees.

Sessions on the importance of *in vitro* data include:

Monday 9:00 a.m. – 12:30 p.m. — The U.S. Tox21 Collaboration: Advances Made and Lessons Learned

Tuesday 1:30 - 4:15 p.m. — Incorporating *In Vitro* Pharmacokinetic Data and Tools into Toxicity Testing and Risk Assessment: State of the Science.

Don't forget to stop by the **NIEHS/NTP exhibit at space 2228** to meet program staff, pick up new science materials, and learn more about free resources on our websites, such as the NTP Nonneoplastic Lesion Atlas.

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

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Occupational health insights into environmental exposures

By Shannon Whirledge

The staggering number of chemicals registered for use in the U.S. — currently 80,000, with 2,000 new compounds introduced each year — suggests that human exposure risks may be largely underappreciated.

Manijeh Berenji, M.D., an occupational medicine specialist at Duke University, knows firsthand that exposures are common and can have a significant impact on health. She focused on the facts of environmental exposures in a Jan. 29 seminar titled "Environmental Exposures and Impact on Reproductive Health: Current Knowledge and Future Directions," hosted by Linda Birnbaum, Ph.D., director of NIEHS and the National Toxicology Program.

According to Berenji, the American Chemical Society estimates that chemicals are currently used in approximately 96 percent of manufactured materials and products. From 1970 to 1995, the production of synthetic organic chemicals tripled, from 50 million to 150 million tons. This increase has contributed to an environment where numerous chemical compounds have not been vigorously tested for all types of toxicity, including reproductive toxicity.

Berenji's seminar allowed NIEHS researchers to see chemical exposures through a clinical lens. (Photo courtesy of Steve McCaw)

Women in the workforce

In the last 40 years, the number of women in the workplace has more than doubled, from 30 million in 1970 to 67 million in 2007. Berenji noted that preconception and *in utero* exposures to toxic chemicals are associated with adverse outcomes at birth, including decreased fetal growth, preterm delivery, low birth weight, and birth defects. Furthermore, certain chemical exposures can lead to health consequences in offspring, as with dichlorodiphenyltrichloroethane (DDT). Although it is no longer used in this country, DDT may still be present in a significant portion of the population due to its persistence in the environment.

Understanding reproductive toxicity is a challenging task. According to Berenji, the gold standard for clinical research is the randomized control trial, in which study participants are randomly chosen to receive a certain treatment or exposure and are then compared to a control group. Because this is not an option when studying human chemical exposure, clinicians and scientists rely on animal models and epidemiological studies.

As an example, Berenji cited the Boston Birth Cohort, a study of an inner city, predominately African-American population that found levels of mercury in fetal cord blood 1.5 times higher than those found in maternal blood. Results indicated that *in utero* exposure to mercury may be underestimated, and the findings suggest that our understanding of chemical exposure risk is still developing.

Birnbaum suggested that Berenji's first-hand knowledge of the impact of chemical exposures would allow for rich collaborations with NIEHS researchers. (Photo courtesy of Steve McCaw)

Agricultural workers and pesticide use

According to Berenji, approximately 1.1 billion pounds of pesticides were used in the U.S. in 2006 and 2007, and agricultural workers experience especially persistent exposures. Of the 19,881 pesticide products registered in the U.S., more than 100 are listed as human neurotoxicants. Furthermore, pesticide exposure is linked to a greater risk of cancer, including breast, prostate, multiple myeloma, and leukemia.

During her residency at the University of California, San Francisco, Berenji taught agricultural workers in Salinas, California, about routes of exposure and measures they could take to minimize exposures. For example, she said, agricultural workers could reduce levels of exposure up to 80 percent simply by using chemically resistant gloves.

From left, Thad Schug, Ph.D., of the NIEHS Population Health Branch; Joel Abramowitz, Ph.D., special assistant to the NIEHS Deputy Scientific Director, Jerry Heindel, Ph.D., also of the Population Health Branch; and Janet Hall, M.D., with Clinical Research Program, followed the seminar with interest and helped generate a thoughtful discussion. (Photo courtesy of Steve McCaw)

Berenji concluded by reviewing case studies that illustrated the need to determine routes of exposure — whether by skin, inhalation, ingestion, or mucous membrane — and to identify the proper medical specialists to involve. She emphasized the value of collaborations between clinicians and researchers, such as those at NIEHS, in developing a more complete understanding of consequences of chemical exposure.

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

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SRP network helps parents understand vapor intrusion in schools

By Carol Kelly

NIEHS-funded experts on vapor intrusion joined a meeting Feb. 9 in Winston-Salem, North Carolina, to educate communities in two schools located over contaminated groundwater about potential health effects of chemical exposures.

After learning that harmful chemicals could be seeping into the air inside Hanes Magnet and Lowrance Middle Schools, parents were naturally concerned about the effects of air quality on their children's health. During the meeting with parents and school officials, grantees from the NIEHS Superfund Research Program (SRP), answered questions about the chemicals and the process of vapor intrusion into classrooms at the schools.

"This event serves as a model for community engagement in response to serious environmental health situations, and it reinforces the value of research networks that incorporate scientific information from health and engineering fields," said Heather Henry, Ph.D., a health science administrator for the NIEHS SRP. "This assistance effort — from the discovery to the parents' forum — unfolded within a matter of weeks. It would not have happened without existing networks among the SRP Centers."

Vapor intrusion

EPA defines vapor intrusion as the migration of vapors from volatile compounds into occupied buildings, from underlying contaminated groundwater or soil. Assessment methods include sampling groundwater, soil gas, and indoor air, but determining environmental risk is complex. For instance, indoor air concentrations are known to fluctuate daily, so assessing long-term exposures using samples that are collected only a few times can be difficult. In addition, sources of chemicals detected in indoor air can be uncertain, due to the use of consumer products that contain the same chemicals as the vapor intrusion.

Vapor intrusion can be a challenging environmental and health issue for regulators, industry leaders, and concerned residents alike.

The public learned that the schools sit above groundwater containing the chemicals trichloroethylene and tetrachloroethylene as the school district was considering plans to build a new facility at the site. Both chemicals are industrial de-greasers — previously used at a factory across the street from the schools — that are linked to several illnesses and considered by the U.S. Environmental Protection Agency (EPA) as likely to cause cancer. The process by which chemicals turn into gaseous substances and rise and enter indoor air is called vapor intrusion (see sidebar).

Calling in a network of experts

To provide parents with expert advice, Kathleen Gray, the research translation leader for the University of North Carolina at Chapel Hill (UNC) SRP, coordinated input from the following scientists:

- **Kelly Pennell, Ph.D.**, a vapor intrusion researcher from the University of Kentucky SRP
- **Wendy Heiger-Bernays, Ph.D.**, an environmental health professor with the Boston University SRP
- **Lenny Siegel**, executive director of the Center for Public Environmental Oversight, where he educates communities on vapor intrusion detection and cleanup

From left, Pennell, Gray, Kat Bawden, UNC research translation team member, Siegel, Henry, Traci Connor, a parent who organized the event, and Dana Haine, UNC research translation team member, posed together at SciWorks museum, where the community meeting was held. (Photo courtesy of Heather Henry)

"This coordinated effort to provide technical assistance represents how well the SRP functions as a research-focused, solution-oriented program," said William Suk, Ph.D., director of the SRP at NIEHS. "It really helped the community to have environmental health experts from three grantees available to help fill knowledge gaps."

Weighing options

In Winston-Salem, the decisions at hand involved whether to relocate students and whether to construct a new facility on a site with known vapor intrusion. "Decision making can be complicated by a lack of data to determine the risk for toxic exposure," said Pennell. "The real challenge of dealing with vapor intrusion is having to make a decision in real time when you don't have all the information you need."

After weighing options and considering available risk assessment information and public opinion, the school board decided to close the schools in question and relocate students. More extensive environmental testing will be conducted to inform future use of the site.

"We will continue dialogue with community members and have offered to help interpret future sampling data as it becomes available," said Gray. "Also, because it is often difficult for the public to sift through what can be overwhelmingly complex information, we've already set up a page on our UNC website that provides this community and others with a one-stop-shopping information resource about vapor intrusion."

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

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Clinical Feature

The Precision Medicine Initiative

By Robin Arnette

During this year's State of the Union address, President Obama announced a $215 million funding commitment to the National Institutes of Health (NIH), the U.S. Food and Drug Administration, and the Office of the National Coordinator for Health Information Technology, to find health solutions for all Americans.

The investment will allow physicians and researchers to take a closer look at specific differences in people's genes, microbiomes, environments, and lifestyles. Through this knowledge, they hope to move the concept of tailored treatments for individuals into everyday practice.

Linked video:

Watch Jo Handelsman, Associate Director for Science in the Office of Science and Technology Policy, describe the Precision Medicine Initiative and its significance. (1:44)

(Launches in new window)

Download Media Player: Flash

This new enterprise is called the Precision Medicine Initiative, and it will support a national network of scientists, focused on cancer in the short-term, and a whole range of health issues and diseases in the long-term. It is a new model of research, built on developments in biomedicine and technology. As NIH Director Francis Collins, M.D., Ph.D., and National Cancer Institute Director Harold Varmus, M.D., wrote in their New England Journal of Medicine opinion editorial, "We believe that the time is right for this visionary initiative, and the NIH and other partners will work to achieve this vision."

Two-phased approach

Biomedical research has made great strides in deciphering the genomic signatures of cancers and developing targeted therapies, but much work remains. In phase one, the Precision Medicine Initiative seeks to develop a deeper understanding of many more cancers, while expanding clinical trials with novel designs. In addition, building a cancer knowledge network that stores all of this data in a usable, digital format will help scientists figure out drug resistance and how to combine therapies for maximum effect.

Once this foundation is established, the second component of the Precision Medicine Initiative will begin. Scientists plan to recruit more than a million Americans to participate in research studies, to better assess disease risk, understand what causes disease, and predict optimal therapies and prevention.

Click here for enlarged image

NIEHS and National Toxicology Program Director Linda Birnbaum, Ph.D., believes bringing together biologists, physicians, technology developers, data scientists, and especially the public will lead to groundbreaking discoveries.

"Can you imagine what we could achieve if we all pull together and contribute our time and expertise to the process?" Birnbaum asked. "We could finally see the full impact of precision medicine on human health."

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"What is needed now is a broad research program to encourage creative approaches to precision medicine, test them rigorously, and ultimately use them to build the evidence base needed to guide clinical practice," wrote Collins, above, and Varmus in the New England Journal of Medicine. (Photo courtesy of NIH)

Science Notebook

NIEHS-supported researchers map epigenome of more than 100 tissue and cell types

By Joe Balintfy

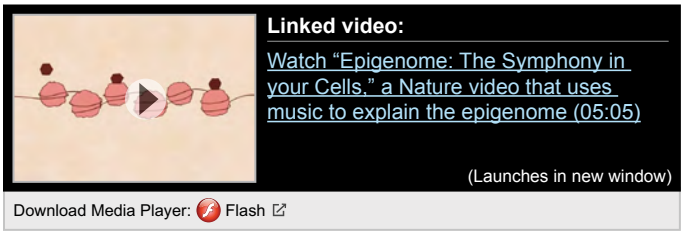
NIEHS grantees, supported by the National Institutes of Health (NIH) Common Fund's Roadmap Epigenomics Program, have mapped the epigenomes of more than 100 types of cells and tissues, providing new insight into which parts of the genome are used to make a particular type of cell. The epigenome is part of the machinery that helps direct how genes are turned off and on in different types of cells.

Much like mapping the human genome laid the foundations for understanding the genetic basis of human health, these new maps of the human epigenome may further unravel the complex links between DNA and disease.

"This represents a major advance in the ongoing effort to understand how the 3 billion letters of an individual's DNA instruction book are able to instruct vastly different molecular activities, depending on the cellular context," said NIH Director Francis Collins, M.D., Ph.D. "This outpouring of data-rich publications, produced by a remarkable team of creative scientists, provides powerful momentum for the rapidly growing field of epigenomics."

Researchers from the Roadmap Epigenomics Program published Feb. 19 a description of the epigenome maps in the journal Nature. More than 20 additional papers, published in Nature and Nature-associated journals, show how these maps can be used to study human biology.

"What the Roadmap Epigenomics Program has delivered is a way to look at the human genome in its living, breathing nature from cell type to cell type," said senior author Manolis Kellis, Ph.D., professor of computer science at the Massachusetts Institute of Technology, and an NIEHS grantee.



"Epigenomics represents the next phase in our understanding of genetic regulation of health and disease," Collins said. (Photo courtesy of NIH)

Chadwick was interviewed about the epigenome papers by major media outlets including the Boston Globe, PBS Newshour, and Reuters. (Photo courtesy of Steve McCaw)

Understanding epigenomics

Almost all human cells have identical genomes that contain instructions on how to make the many different cells and tissues in the body. During the development of different types of cells, regulatory proteins turn genes on and off and, in doing so, establish a layer of chemical signatures that make up the epigenome of each cell. In the Roadmap Epigenomics Program, researchers compared these epigenomic signatures and established their differences across a variety of cell types. The resulting information can help us understand how changes to the genome and epigenome can lead to conditions such as Alzheimer's disease, cancer, asthma, and fetal growth abnormalities.

"This is the most comprehensive catalog of epigenomic data from primary human cells and tissues to date," said Lisa Chadwick, Ph.D., project team leader and program director at NIEHS. "This coordinated effort, along with uniform data processing, makes it much easier for researchers to make direct comparisons across the entire data set."

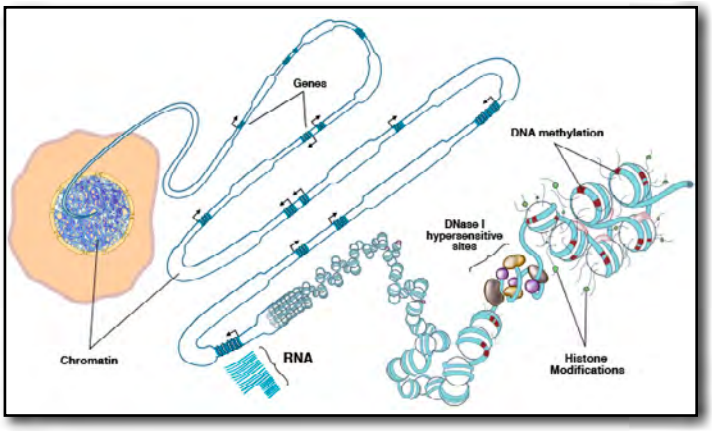
The data, available to the biomedical research community, can be found at the National Center for Biotechnology Information website.

The value of epigenomic data

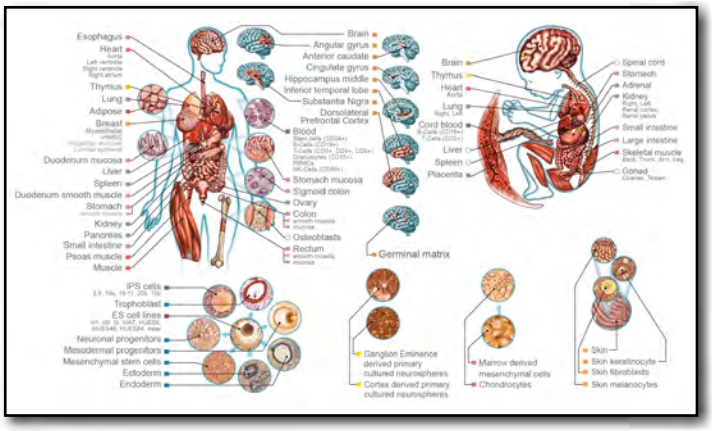
Researchers can now take data from different cell types and directly compare them. "Today, sequencing the human genome can be done rapidly and cheaply, but interpreting the genome remains a challenge," said NIEHS grantee Bing Ren, Ph.D., professor of cellular and molecular medicine at the University of California, San Diego, and co-author of the Nature paper and several of the associated papers. "These 111 reference epigenome maps are essentially a vocabulary book that helps us decipher each DNA segment in distinct cell and tissue types. These maps are like snapshots of the human genome in action."

"Researchers from the 88 projects supported by the program, including those from this recent series of papers, have propelled the development of new epigenomic technologies," said John Satterlee, Ph.D., co-coordinator of the Roadmap Epigenomics Program, and program director at the National Institute on Drug Abuse (NIDA), part of NIH. Satterlee added that the work of this program has served as a foundation for continued exploration of the human epigenome through the International Human Epigenome Consortium.

NIDA, NIEHS, and the National Institute on Deafness and Other Communication Disorders are co-administrators of the NIH Common Fund's Epigenomics Program.



An epigenomic signature can be made on the genome in two ways, both of which play a role in turning genes off or on. The first occurs when chemical tags called methyl groups are attached to a DNA molecule directly (DNA methylation). The second occurs when a variety of chemical tags attach to the tails of histone proteins that package DNA (histone modifications). (Image courtesy of John Stamatoyannopoulos and Rae Senarighi) Click image to enlarge



Reference epigenomes are available for more than 100 cell and tissue types. (Image courtesy of Nature and Roadmap Epigenomics Consortium) Click image to enlarge

Citation: Roadmap Epigenomics Consortium. 2015. Integrative analysis of 111 reference human epigenomes. Nature 518(7539):317-330.

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

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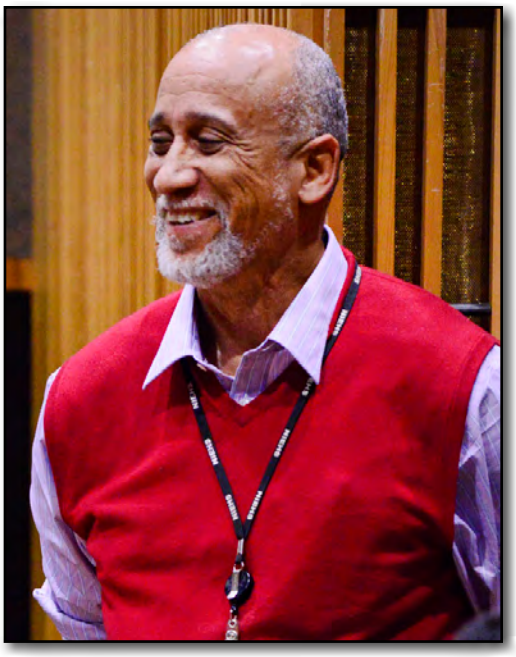
Epigenetics workshop features wide range of cutting-edge research

By Kelly Lenox

Researchers working at the intersection of epigenetics and environmental health sciences came together Jan. 23 for a minisymposium at NIEHS. Participants, who represented a diverse range of work supported by the institute's three research divisions, discussed their latest findings and developed potential collaborations.

"Our goal was two-fold," said Fred Tyson, Ph.D., a program director in the Division of Extramural Research and Training and a co-chair of the NIEHS epigenetics faculty. "We wanted to increase communication across the divisions of NIEHS and to promote collaborative science," he said. Moderators, speakers, and attendees from across the institute and across the country (see sidebar) enjoyed a fruitful exchange of ideas and queries, leading Tyson to affirm that the goals were indeed met.



Tyson was lead organizer of the minisymposium. He is a program director of the NIH Roadmap Epigenomics Program and oversees a portfolio of grants for the NIEHS Division of Extramural Research and Training, many of which focus on environmental genetics. (Photo courtesy of Steve McCaw)

How cells remember and forget their past

"When we think about epigenetics, we're really thinking about gene memory over time," said Howard Chang, M.D., Ph.D., as he discussed his cutting-edge work on long noncoding RNAs. "What's very mysterious is how a signal causes a gene to stay on after a transient exposure, without the persistent presence of the signal." Chang's research suggests that long noncoding RNA is both a guide and a timer for epigenetic modification. In Chang's words, "RNA helps cells remember and forget their past."

As he concluded, Cheryl Walker, Ph.D., acknowledged the diverse interests of the gathered researchers. "That was one of the best talks I've ever heard, and thank you to NIEHS, because I'm not sure I would have been in the room to hear it any other place," she said.

Across the sexes, across time

Other presentations emphasized that when environmental exposures cause epigenetic modifications, the effects can be far-reaching. Walker's work explores the hypothesis that early life exposures to endocrine-disrupting chemicals can directly modulate the activity of the epigenome, reprogram it, and increase the susceptibility to disease across the lifespan.

Variables that affect epigenetic modification include not just time, but sex, according to Max Costa, Ph.D., who discussed the effects of arsenic and nickel exposures. “There’s a huge difference between the sexes in the effects of arsenic on gene expression,” he said.

Diana Laird, Ph.D., pointed out that the field of transgenic epigenetic inheritance calls for new language. For the first time, Laird shared the data emerging from her research on germ cells. She distinguished between multigenerational exposures, in which both an adult female and the eggs she carries might be affected, and transgenerational exposures, in which exposure of a pregnant female affects the germ cells of a fetus, thus affecting the granddaughter generation.

According to Laird, such alteration of germ cell lines has been seen from exposure to several endocrine-disrupting chemicals. Laird was a 2010 recipient of the National Institutes of Health (NIH) New Innovator Award, which is awarded to support highly innovative approaches to major contemporary challenges in biomedical research.

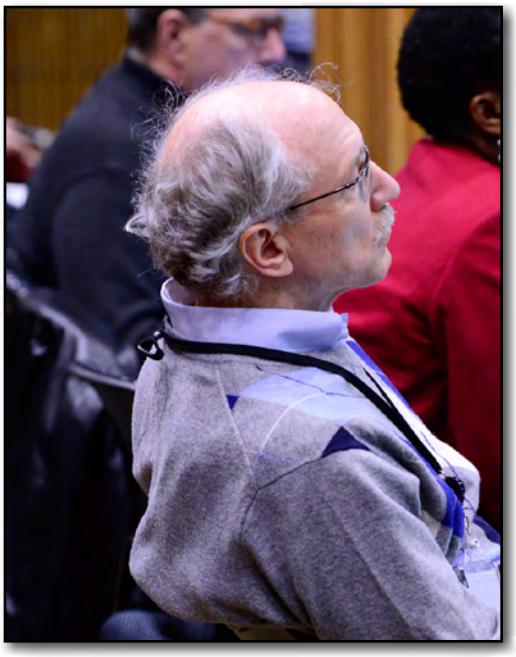
Lisa Chadwick, Ph.D., moderated the morning session. She is also a program director of the NIH Roadmap Epigenomics Program. (Photo courtesy of Steve McCaw)

Across the spectrum

A variety of techniques and lines of inquiry characterized the day, from the NIEHS Division of the National Toxicology Program (NTP) systematic review of epigenetic studies, described by Katie Pelch, Ph.D., to the talk by Guang Hu, Ph.D., on the INO80 chromatin remodeling complex and its role in regulating the pluripotency of embryonic stem cells, that is, their ability to differentiate into a variety of tissue types.

In closing comments, John Bucher, Ph.D., associate director of DNTP, noted NIH’s interest in increasing in-house researcher and grantee interactions. “Epigenetics is an area that is coming together and showing a great synergy because of this interaction,” he said. “This is a terrific example for the other institutes at NIH to follow.”

Bill Schrader, Ph.D., NIEHS deputy scientific director, framed his closing comments in the context of the evolving nature of the epigenetics field. “Having the techniques available allows the really complicated questions to be asked,” he said, ending with a challenge to the participants. “Always be thinking how you can push the envelope for better tools.”



Rick Woychik, Ph.D., is the deputy director of NIEHS and also heads the NIEHS Mammalian Genome Group. (Photo courtesy of Steve McCaw)

Walker spoke of enjoying her visit to NIEHS, where she was a research fellow in the 1980s. (Photo courtesy of Steve McCaw)

Trevor Archer, Ph.D., left, head of the NIEHS Chromatin and Gene Expression Group and moderator of the afternoon session, shared a light moment with grantee Walker, right. (Photo courtesy of Steve McCaw)

NIEHS Eukaryotic Transcriptional Regulation Group head Paul Wade, Ph.D., like the other presenters, was active in the question and answer sessions that sparked lively exchanges among the scientists. Wade co-chairs the epigenetics faculty with Tyson. (Photo courtesy of Steve McCaw)

"An invisible hand keeping a gene in an on or off state is the mechanism behind epigenetics and the concept of gene memory over time," said Chang. (Photo courtesy of Steve McCaw)

Raymond Tice, Ph.D., former head of the NIEHS Biomolecular Screening Branch, attended the full day meeting despite his impending retirement. (Photo courtesy of Steve McCaw)

NIEHS Cross-divisional Minisymposium on Epigenetics

Moderators:

Lisa Chadwick, Ph.D., NIEHS Division of Extramural Research and Training

Trevor Archer, Ph.D., NIEHS Epigenetics & Stem Cell Biology Laboratory

Presenters:

Howard Chang, M.D., Ph.D., Stanford University School of Medicine — "Genome Regulation by Long Noncoding RNAs"

Max Costa, Ph.D., New York University Langone Medical Center — "Arsenic Carcinogenesis and Interference With Histone mRNA Processing"

Guang Hu, Ph.D., NIEHS Epigenetics & Stem Cell Biology Laboratory — "INO80-dependent Chromatin Remodeling in ESC Self-renewal and Pluripotency"

Diana Laird, Ph.D., University of California, San Francisco School of Medicine — "Germ Cell Development and Transgenerational Inheritance in Mice"

Katherine Pelch, Ph.D., NTP Office of Health Assessment and Translation — "Environmental Influences on the Epigenome: Using SWIFT Text Mining Tool to Assess the Current State of the Science"

Brian Strahl, Ph.D., University of North Carolina School of Medicine — "Chromatin Mechanisms That Underlie DNA Methylation Inheritance"

Paul Wade, Ph.D., NIEHS Epigenetics & Stem Cell Biology Laboratory — "Transgenerational Inheritance of DNA Methylation in the Mouse"

Cheryl Walker, Ph.D., Texas A&M Health Science Center — "Developmental (Re)Programming: Cross-talk Between Environmental Exposures and the Epigenome"

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NIEHS-NCI collaboration leads to novel analysis of anticancer therapeutics

By Monica Frazier

Scientists at NIEHS collaborated with National Cancer Institute (NCI) researchers to assess the therapeutic results of combination anticancer treatments. Their findings, published online Jan. 12 in the journal Frontiers in Genetics, demonstrated the potential for their toxicogenomics approach to predict toxicity risks of cancer therapies that use a combination of drugs.

Synergistic expertise across NIH campuses

Pierre Bushel, Ph.D., staff scientist in the Biostatistics and Computational Biology Branch, led the NIEHS team. His group developed the novel Extracting Patterns and Identifying co-Expressed Genes (EPIG) methodology, one of several bioinformatics tools developed at NIEHS.

Myrtle Davis, Ph.D., chief of the Toxicology and Pharmacology Branch at NCI, noted that she first came to know of Bushel's work through a 2010 article in the National Institute of Health (NIH) newsletter The NIH Catalyst. The analytical approach Bushel's group used matched perfectly with what her group sought for in their studies on combination anticancer agents. "The research effort of NIEHS in bioinformatics and our NCI program focus on effects of anticancer therapy were highly synergistic," Davis said.

Bushel noted that other NIH staff played a role in the collaboration, including Elaine Knight, Ph.D. and Sandy Eldridge, Ph.D., from NCI, and Jianying Li at NIEHS. (Photo courtesy of Steve McCaw)

The sequence of chemotherapeutics matters

Treating cancer typically requires a combination of drugs. Combination treatments often have more severe toxicity and undesirable side effects, leading clinicians to reduce dosages. Bushel and Davis sought to use a systems-based computational approach to perform a nonclinical assessment of combination treatments. As proof of principle, they studied two well-known and commonly used chemotherapy drugs, topotecan and oxaliplatin.

Bushel and Davis hypothesized that they could use early responses of messenger RNA in tissues, after a single dose of one drug alone and after dosing with the second drug, to infer enhanced toxicity. Their hypothesis proved correct. The researchers found that a single dose of topotecan resulted in bone marrow lesions after 1 hour. Oxaliplatin alone did not result in such lesions until 6 hours after treatment. When a combination therapy was used, lesions were more severe when topotecan was administered first.

Using EPIG analysis, the scientists identified the prominent pathways within bone marrow affected after treatment with the two drugs. These included genes that alter bone marrow histone biology, chromatin remodeling, DNA repair, bone regeneration, and respiratory and oxidative phosphorylation. In particular, the up-regulation of DNA repair and chromatin remodeling pathways are in line with the known mechanism of topotecan's toxicity as an inhibitor of the enzyme topoisomerase I.

The pair of investigators intend to extend this work. "The success of the collaboration on the bone marrow data set will certainly carry over to investigate the oxaliplatin-topotecan combination effect on gene expression in other rat tissues," said Bushel. "In the long run, we are hoping to reveal a few mechanistic signatures that may be applied *in vivo* or *in vitro*," Davis added.

"A nonclinical option can supplement the current therapeutic strategy by providing means to determine when combination toxicity presents a high risk," said Davis. "Or it might help identify risks to organs from combination therapy, which wouldn't be expected from the single drug profiles, so that clinicians could closely monitor them." (Photo courtesy of Myrtle Davis)

Citation: Davis M, Li J, Knight E, Daniels KK, and Bushel PR. 2015. Toxicogenomics profiling of bone marrow from rats treated with topotecan in combination with oxaliplatin: a mechanistic strategy to inform combination toxicity. Front Genet [online 12 Jan 2015; doi 10.3389/fgene.2015.00014].

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

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Seminar highlights emerging biomarkers of inflammation

By Maile Henson

The NIEHS Cross-Divisional Inflammation Faculty held a seminar and panel discussion webcast Feb. 5 on improving risk identification and treatment monitoring in heart and lung disease.

The seminar featured three experts who presented their work on advances in identifying and validating predictive markers of inflammation, along with new approaches to discovering novel biomarkers of inflammation.

Gong was the only keynote speaker on site and one of five participants in the panel. Wang, Bowler, and Miller spoke via remote connection. (Photo courtesy of Steve McCaw)

- Thomas Wang, M.D., professor of medicine and director of cardiovascular medicine at the Vanderbilt Heart and Vascular Institute, focused on the search for more predictive markers of cardiometabolic disease risk and progression.
- Russell Bowler, M.D., Ph.D., professor of medicine in the Division of Pulmonary, Critical Care and Sleep Medicine at National Jewish Health, explored the search for biomarkers specific to the phenotypes, or physiological manifestations, of chronic obstructive pulmonary disease (COPD).
- Jicheng Gong, Ph.D., postdoctoral researcher in the laboratory of Junfeng Zhang, Ph.D., at the Duke University Nicholas School of the Environment, described his group's studies of biomarkers of respiratory disease risk from particulate air pollution.

Shared concerns about meaningful predictive biomarkers

As Wang explained early in the program, most people who develop cardiovascular disease have few, if any, of the traditional biomarkers of disease. "This missing predictiveness," he said, "is the underlying motivation for clinical biomarker research in cardiology."

Clinicians are concerned, he added, that other unknown factors at the tissue level are involved, and that too often, biomarkers are not informative because they correlate more closely with each other than with the disease itself.

Wang introduced the theme of unbiased searches for biomarkers, which was developed in greater detail by Bowler, who is both a clinician and a computational biologist. He described the search for informative biomarkers in three phenotypes of COPD using several platforms.

"Size matters," Bowler said, as he described an integrated approach to large-scale searches for biomarkers with stronger predictive value. "The size of the cohorts keeps growing," he added, "[and] convergence is really the future."

Closing out the presentation portion of the program with a move to the environmental side, Gong described studies of air pollution exposures before, during, and after the summer 2008 Beijing Olympics. During a brief window of time that summer, restrictions on traffic and manufacturing helped create a natural laboratory for studies of exposure, with an unprecedented control of environmental variables. Gong reported on the measurement of biomarkers of inflammation along four different pathways and correlated their levels with particulate sizes and systemic effects.

The people behind the seminar

Event hosts:

- Christine Parks, Ph.D., of the Epidemiology Branch;
- Mike Fessler, M.D., head of the Clinical Investigation of Host Defense Group;
- Srikanth Nadadur, Ph.D., lead for nanotechnology program grants; and
- Nina Jaitly, M.D., extramural scientific program manager.

A panel discussion moderated by Nadadur followed the talks, and featured the three speakers, along with:

- NIEHS clinical researchers Fred Miller, M.D., Ph.D., and Shepherd Schurman, M.D., and epidemiologist Bonnie Joubert, Ph.D.;
- National Toxicology Program toxicologist Andy Rooney, Ph.D.; and
- Grantee Sven-Eric Jordt, Ph.D., of Duke University, who studies acute respiratory exposures.

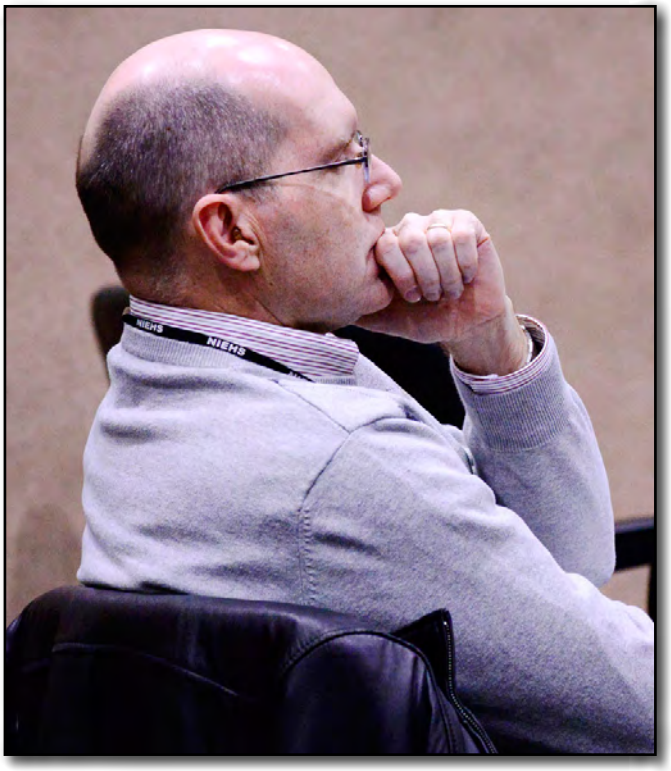
Take-home messages

Diversity among the panelists in the seminar provided a refreshing cross-divisional perspective on a discussion about the translational implications of inflammatory biomarkers for human health, challenges in the field, and opportunities to use the information to advance the faculty's mission to improve NIEHS intramural, extramural, and toxicology programs (see text box).

(Maile Henson, Ph.D., is an Intramural Research Training Award fellow in the NIEHS Synaptic and Developmental Plasticity Group. She is currently on a detail assignment in the NIEHS Division of Extramural Research and Training.)

"I want you to weigh in on both untargeted approaches and a candidate gene approach towards identifying biomarkers," Nadadur instructed the panelists, "what you've learned, what are the opportunities, and what are the challenges." (Photo courtesy of Steve McCaw)

As Jordt, right, looked on, panelist Joubert, left, addressed the standardization of measurements across studies in meta-analysis, as epidemiologists try to increase the statistical power of their research by integrating existing data sets from other studies. (Photo courtesy of Steve McCaw)



During the panel discussion, members of the audience, such as NIEHS inflammation grants administrator Mike Humble, Ph.D., left, listened as Bowler lamented the variability in studies. "Particularly in metabolomics, every laboratory does things a little bit differently." (Photo courtesy of Steve McCaw)

In the search for informative biomarkers, framing the right question is an important first step. "How do we identify those nonoverlapping factors?" Rooney asked, as the discussion turned to what makes a biomarker more specific to a disease. (Photo courtesy of Steve McCaw)

Schurman posed another question that needed to be answered from a clinician's standpoint. "What [do] biomarkers do in response to treatment, in correspondence to how the disease is doing?" he asked. "What's the correlation to treatment?" (Photo courtesy of Steve McCaw)

Breaking down silos and supporting collaborations

The NIEHS Cross-Divisional Inflammation Faculty is charged with implementing the institute's Strategic Plan focus on one of the six high-priority areas of public health concern — environmentally associated inflammation.

The overarching goal of the inflammation faculty is to coordinate the institute's scientific and leadership resources to address current state-of-the-science and advance understanding of the role of environmental exposure in inflammation. Shifting direction, from the culture of individual silos to building cross-divisional and transdisciplinary collaborations, requires a great deal of effort, but should produce major benefits for everyone involved.

By providing activities such as the Inflammation Faculty Seminar/Webcast Series, panels, and roundtable discussions, the group is enhancing communication among the three NIEHS research divisions. Along with the series of state-of-the-science seminars, a future workshop will provide a forum for discussion of emerging concepts in the inflammation field and definition of knowledge gaps that will inform NIEHS leadership of divisional research programs.

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Study adds to understanding of respiratory syncytial virus disease

By Eddy Ball

A new study, funded in part by NIEHS, offers insight into the network of mechanisms involved in triggering a life-threatening respiratory disease in infants, respiratory syncytial virus (RSV) bronchiolitis, which is an important public health issue worldwide.

The result is what researchers describe as a plausible definition of the mechanisms involved in the interaction of environmental, genetic, epidemiological, and immune factors in the development of the disease in infants. The study takes into account the broad range of environmental factors, which include the effects of viral load, compounding bacterial and irritant exposures, and socioeconomic status on host susceptibility.

The pan-American team of 43 scientists also presents new evidence related to the hygiene hypothesis, which suggests that over-sanitizing the environment doesn't necessarily lead to better outcomes in every aspect of an infant's health. Avoiding some level of exposure may, in fact, interfere with conditioning of the immune response to infection and worsen disease.

For one group of middle class children with variations in the gene encoding toll-like receptor 4 (TLR4), cleaner living seemed to have little impact on the disturbing rates of their hospitalization, which approached those of extremely premature babies.

International team science at work

Co-led by NIEHS lead researcher Steven Kleeberger, Ph.D., and his long-time colleague Fernando Polack, M.D., an infectious disease specialist with appointments at Vanderbilt University and the Infant Foundation in Argentina, the paper appeared in the February issue of the Journal of Clinical Investigation.

"We looked at hundreds of infants from different environments, performed a battery of tests on a wide range of molecules, and confirmed our findings in a mouse model of RSV disease," Kleeberger said. "While controversies remain about RSV, we've helped to answer a number of important questions and identified a novel group at high risk for developing a severe form of the disease."

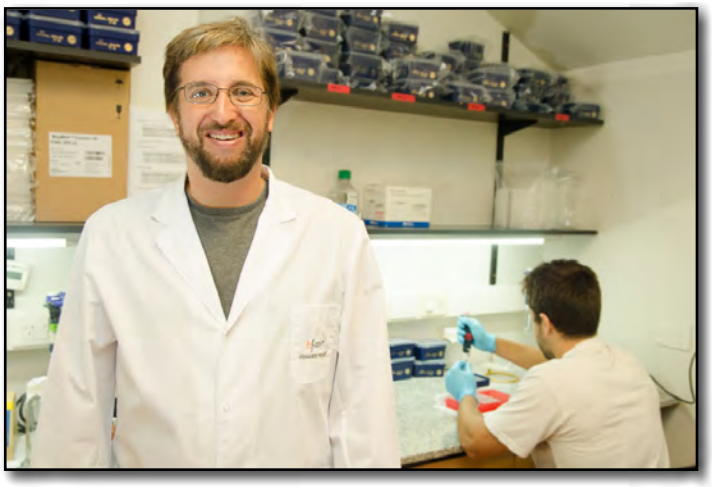
Through a careful process of elimination, the team narrowed down the influences of a number of inflammatory proteins to identify the specific cytokines involved. The researchers also examined candidate variables that might affect the severity of RSV bronchiolitis, including levels of the virus in respiratory secretions, which did not show a significant association.

Kleeberger took advantage of collaborations with Polack and his large cohort of children in Argentina to add considerable power to work on infant respiratory diseases. (Photo courtesy of Steve McCaw)

Pioneering tie-in of environment and RSV

According to the researchers, this is the first study of its size and kind to explore the role of environmental factors in RSV pathogenesis. The findings point to involvement of environmental endotoxin, Tlr4 genotype, and cell polarization of T helper type 2 (Th2) as influencing disease severity. They also gained insight into the immune mechanism regulating differential susceptibility to RSV disease severity.

Their findings, the team concluded, point to the importance of exploring modulation of these target molecules. They also speculated that additional research with Tlr4 genotype infants could lead to preventive interventions aimed at virus neutralization and novel anti-Th2 approaches to help protect children at highest risk of severe disease.



Polack, shown in his lab in Buenos Aires, led access to patients at four hospitals in different regions the city, two of them separated by more than 40 miles. (Photo courtesy of Fundacion INFANT)

Along with NIEHS funding, which included the Director's Challenge Award Kleeberger and Polack received in 2006 (see story), the study was supported by the National Institute of Allergy and Infectious Diseases and the Bill and Melinda Gates Foundation.

The team included scientists affiliated with 17 different groups in the U.S. and Argentina, and a hospital in Brazil. Two additional NIEHS scientists, biologist Jacqui Marzec and biostatistician Min Shi, M.D., Ph.D., were also part of the team.

Citation: Caballero MT, Serra ME, Acosta PL, Marzec J, Gibbons L, Salim M, Rodriguez A, Reynaldi A, Garcia A, Bado D, Buchholz UJ, Hijano DR, Coviello S, Newcomb D, Bellabarba M, Ferolla FM, Libster R, Berenstein A, Siniawaski S, Blumetti V, Echavarria M, Pinto L, Lawrence A, Ossorio MF, Grosman A, Mateu CG, Bayle C, Dericco A, Pellegrini M, Igarza I, Repetto HA, Grimaldi LA, Gudapati P, Polack NR, Althabe F, Shi M, Ferrero F, Bergel E, Stein RT, Peebles RS, Boothby M, Kleeberger SR, Polack FP. 2015. TLR4 genotype and environmental LPS mediate RSV bronchiolitis through Th2 polarization. J Clin Invest 125(2):571-582.

Marzec is a member of Kleeberger's Environmental Genetics Group at NIEHS. (Photo courtesy of Steve McCaw)

Shi is a member of the NIEHS Biostatistics and Computational Biology Branch, specializing in gene-environment, gene-gene interaction, and pathway-based analysis. (Photo courtesy of Steve McCaw)

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Researcher explores neuro-behavioral effects of endocrine disruption

By Simone Otto

Grantee Andrea Gore, Ph.D., energized her audience Jan. 30 at NIEHS with her talk on "Environmental Endocrine Disruption of the Brain: Past, Present, and Future." Gore, a professor at the University of Texas in Austin, has been a moving force in the Society of Endocrinology for many years as well as editor in chief of the journal Endocrinology.

"We are really excited to have Andrea here both because of her personal science in the lab, and to acknowledge and thank her for all the work she's done in the field of endocrine disruption that has been very important to help NIEHS with our mission," said Jerry Heindel, Ph.D., program administrator in the extramural division at NIEHS, when introducing Gore.

A long time NIEHS grantee, Gore has collaborated on Endocrine Society-sponsored review articles and conferences on endocrine disruptors. Members of the society have also visited NIEHS this year to discuss collaborations.

"We have contaminated our world and we cannot undo it," Gore said at the beginning of her presentation. "We really need to understand what we've done to try to figure out what the health consequences are and to see whether we can fix some of those problems."

Gene expression and changes in the brain

Like other researchers in the field, Gore's experiments with endocrine disruptors, such as Aroclor 1221 (see text box), turned up reproductive effects, such as timing of puberty. But Gore has taken her work a step further, to also explore nonreproductive sex-specific consequences of exposure in different areas of the brain.

Gore subdivided the hypothalamus, testing different regions for neuroendocrine alterations. One gene strongly affected was the estrogen receptor, a gene that according to Gore is disrupted in the hypothalamus at many different ages and also by many different endocrine disrupters.

Currently, Gore is looking for transgenerational effects on gene expression. Since the exposed F0 dam, the initial parent generation in a multigenerational reproduction study, is pregnant and the F1 embryo and F2 germ cells were also exposed to Aroclor 1221, Gore selected the F3 generation for her studies.

"I think the gene expression work is important because we start to identify targets or networks or pathways that we think are particularly perturbed," said Gore in her lecture.

For Gore and NIEHS, the third time was the charm. Her two previously scheduled visits were cancelled — in October 2013 by the government shutdown and in February 2014 by snow. (Photo courtesy of Steve McCaw)

Heindel oversees the NIEHS grant portfolio supporting Gore's work on endocrine disruption, including research that supports the Endocrine Society scientific statement on endocrine-disrupting chemicals, which she coauthored with several other grantees. (Photo courtesy of Steve McCaw)

Exploring sex-linked behaviors affected by endocrine disruption

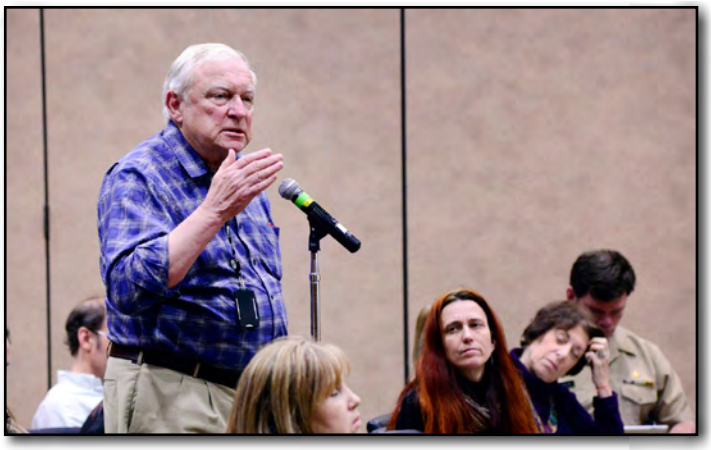
Gore studied how prenatal exposure to endocrine disrupters affects social behavior. She focused on ultrasonic vocalizations and social novelty. For ultrasonic vocalizations, after 2 days of training rats were paired with a receptive partner across a screen. After the partner was taken away their vocalizations were recorded. The exposed group made a different pattern of calls than controls.

Social novelty was tested by time spent and type of behavior exhibited by rats with a new sexual partner versus a familiar one. While control males touched noses more often, males exposed to Aroclor 1221 touched noses less and spent less time with the novel mate than controls, females touched noses more frequently, showing sexually dimorphic changes.

Gore has also studied the mating preference of male and female rats in the F3 generation of rats exposed to another endocrine disruptor, vinclozilin. The F3 males go on to develop germline transmitted diseases, although at the time of testing they were healthy by all measures used.

Gore found that female rats of both the treatment and vehicle lineages preferred the control males over the males from a treatment background, showing both how profound and how subtle the effects of these chemicals can be even on subsequent generations without direct exposure.

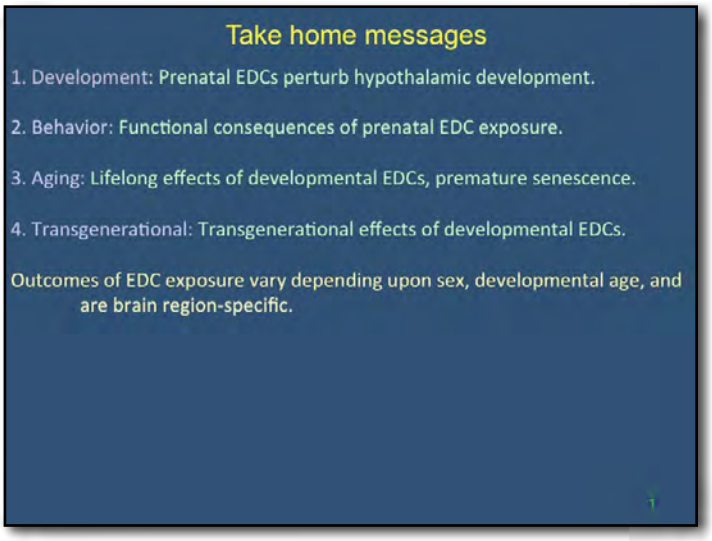
Among members of the audience with questions for Gore was NIEHS and National Toxicology Program (NTP) Director Linda Birnbaum, Ph.D. Birnbaum's lab at NIEHS focuses on endocrine disruption by fire retardant chemicals. (Photo courtesy of Steve McCaw)



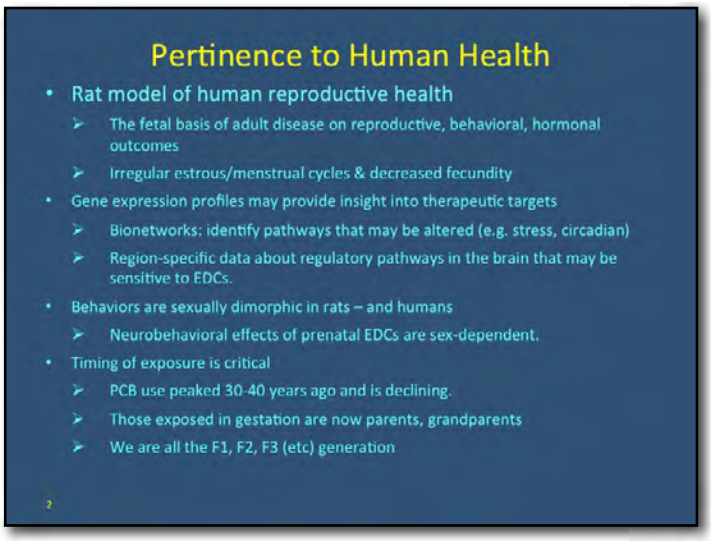
NIEHS Deputy Scientific Director Bill Schrader, Ph.D., asked about experiments related to timing of exposure. "Have you ever given these compounds at a different time and shown that there is no effect because you have avoided that developmental window?" (Photo courtesy of Steve McCaw)

Endocrinologist Janet Hall, M.D., who is involved in clinical research at NIEHS, asked about Gore's future plans to examine interactions among different endocrine disruptors. "Moving into the mixture field is going to be harder than it ought to be," Gore responded. (Photo courtesy of Steve McCaw)

Interested scientists from across NIEHS research divisions included, from left, NTP alternative methods expert Warren Casey, Ph.D.; reproductive and developmental biologists Wendy Jefferson, Ph.D., and Retha Newbold; and grant program manager Cindy Lawler, Ph.D. (Photo courtesy of Steve McCaw)



Click image to enlarge (Image courtesy of Andrea Gore)



Click image to enlarge (Image courtesy of Andrea Gore)

Effects of endocrine disruption on gene and protein expression

Gore used as model pregnant Sprague Dawley rats exposed to vehicle, 3 percent dimethyl sulfoxide in oil; estradiol benzoate, a positive control; or Aroclor 1221, a mixture of polychlorinated biphenyls (PCBs), in 1 or 2 doses at the beginning of the third trimester of pregnancy on day 16 and day 18. PCBs are endocrine disrupters, and endocrine disrupters are defined by the Endocrine Society as an exogenous, or nonnatural, chemical or mixture of chemicals that interferes with any aspect of hormone action. Male and female pups were studied to determine the sexually dimorphic effects of this prenatal exposure.

Gore measured expression of 48 genes in various brain regions and ages. Her work revealed that female genetic expression patterns were masculinized after exposure. Protein expression was altered to an even greater magnitude.

"I think that epidemiological studies in the last few years have come a very long way in contributing to our understanding of relationships or correlations," Gore said of new directions in her research. "Therefore, animal models such as ours are critical for directly testing the cause-and-effect relationships between early life exposures and the manifestation of a dysfunction. Since the hormones and brain pathways that we study in rats are highly conserved with humans, as well as other mammals, we believe that our results will help identify targets for possible interventions."

(Simone Otto, Ph.D., is an Intramural Research Training Award fellow with the NIEHS Ion Channel Physiology Group.)

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NTP presents SAN trimer results at Toms River public meeting

By Robin Mackar

Scientists from the NIEHS Division of the National Toxicology Program (NTP) presented study findings directly relevant to the citizens of Toms River, New Jersey, during a Feb. 4 public meeting on styrene-acrylonitrile trimer, also known as SAN trimer. A byproduct of the manufacture of acrylonitrile styrene plastic, SAN trimer is one of the contaminants at the Reich Farm Superfund site in Toms River.

After the U.S. Environmental Protection Agency (EPA) asked NTP to study the chemical, NTP began an extensive design, study, and peer review process. Results, published in 2012, concluded that SAN trimer did not cause cancer in male or female rats.

EPA invites NTP to public meeting

Prior to the NTP studies, EPA lacked scientific information about the compound. Now, EPA is using the findings, along with other data, to establish cleanup levels for the Superfund site.

Behl is a neurotoxicologist in the NTP Systems Toxicology group. (Photo courtesy of Steve McCaw)

The public meeting was held to inform the community about the toxicology and carcinogenicity study results and planned cleanup levels for SAN trimer in the soil and groundwater.

EPA Region 2 invited toxicologist Mamta Behl, Ph.D., and pathologist Susan Elmore, D.V.M., to discuss the research. "I was very pleased to have the opportunity to represent NTP at this public meeting," Behl said. "It is a very different experience presenting to nonscientists, and it's something we need to do more of." Behl also expressed appreciation for having her pathology colleague Elmore along to explain the rigorous process.

"This is a good example of how NTP findings are being used in a real life setting," said NTP Associate Director John Bucher, Ph.D. "We want our research to be used for public health decision-making, and in this case, EPA used our findings to help establish cleanup levels."

Elmore, staff scientist in the NTP Pathology Group, presented the SAN trimer pathology findings. (Photo courtesy of Steve McCaw)

SAN trimer study results

Behl outlined the study process, from the nomination of the chemical to the publication of final conclusions in NTP Technical Report 573. She explained the rationale for testing in rats, noting that the 2-year bioassay studies are the gold standard for identifying potential human carcinogens.

Behl said the studies were designed to determine whether SAN trimer caused cancer or other toxic effects in rats, following lifetime exposure starting in the womb. As part of the study, pregnant rats and their offspring were fed one of three doses of SAN trimer (400, 800, or 1,600 parts per million). The scientists performed a comprehensive assessment and found no effect on survival or on pregnancy and littering, and no significant increase in cancer.

The public meeting with NTP and EPA staff drew nearly 100 residents from the Toms River area. (Photo courtesy of EPA)

Elmore focused on the pathology process and results. She said that since the nervous system was a potential target for cancer, NTP conducted a more detailed evaluation of the brain, spinal cord, and peripheral nerves than is typically done in 2-year studies. Elmore also described the additional reviews performed to thoroughly evaluate all tumors and other lesions.

In its final conclusions, NTP found no evidence that SAN trimer caused cancer in male and female rats. Some noncancer effects, such as peripheral nerve damage in the exposed male and female rats, were reported.

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

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Yakel engages audience at Duke toxicology seminar

By Simone Otto

NIEHS neurobiologist Jerry Yakel, Ph.D., spoke Feb. 13 at Duke University as part of its Integrated Toxicology and Environmental Health Program spring seminar series.

In his presentation on "The Role of Nicotinic ACh [Acetylcholine] Receptors in Hippocampal Excitability and Plasticity," Yakel explored the connections between his research as head of the Ion Channel Physiology Group and the environmental public health interests of his audience.

"Nicotine has been used as a basis for many pesticides, and neurons that respond to nicotine have known associations with diseases that include schizophrenia, Parkinson's, and Alzheimer's," Yakel said. "The responses of neurons to nicotine have important implications for both toxicology and environmental issues."

Yakel's enthusiasm for his research was obvious as he described experiments to demonstrate the mechanics of neuronal excitability and plasticity. (Photo courtesy of Steve McCaw)

Exploring excitability and plasticity in the brain

To introduce the complexity of neuronal excitability and plasticity, Yakel described the organization of cholinergic input in the brain, the flow of information through the hippocampus, and the nature of synapses, which are the points at which nerve cells pass electrical or chemical signals to other cells. Yakel's research focuses on effects the environment might have on cholinergic neurons and neurons that have cholinergic receptors.

Cholinergic neurons transmit signals to other cells using the neurotransmitter acetylcholine. Cells with receptors that are excited by acetylcholine are also often activated by nicotine, a process the Yakel lab has studied in great detail.

The hippocampus, a part of the brain that is important in learning and memory, has a high volume of input from cholinergic neurons and is a primary area of focus for research in the Yakel lab. The group also conducts research on the basal forebrain, the source of cholinergic input into the hippocampus, and an area that is significantly affected in Alzheimer's disease.

In his experiments on excitability and plasticity, Yakel uses electrophysiological techniques to measure the flow of information through these neurons by recording changes in the current passing through them.

Yakel's presentation drew an attentive audience of students, trainees, and faculty to Field Auditorium at Duke University. (Photo courtesy of Steve McCaw)

Exciting research focuses on the hippocampus

Yakel discussed in some detail three of the exciting areas of research going on in his lab, beginning with studies on how cholinergic neurons modulate hippocampal signaling important for memory consolidation.

He also described research into the timing of acetylcholine release into the hippocampus, which is important for strengthening the connection of nerve cells through synapses. This alteration in synaptic strength is the basis of plasticity and allows the brain to respond to a changing environment. This adaptive process can be compromised in disorders such as schizophrenia.

Another area of the lab's focus is the signaling cascade that occurs when an alpha-7 nicotinic acetylcholine receptor is opened. Better understanding of this response could help to identify therapeutic targets for combating neurological and neurodegenerative diseases.

(Simone Otto, Ph.D., is an Intramural Research Training Award fellow with the NIEHS Ion Channel Physiology Group.)

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Host Ed Levin, Ph.D., professor of psychiatry at Duke, shared the stage with Yakel during the question and answer session that followed the talk. (Photo courtesy of Steve McCaw)

This month in EHP

The March issue of Environmental Health Perspectives (EHP) examines what happens to discarded furniture treated with problem flame retardants, and the implications of a new, genetically diverse mouse model.

http://twitter.com/ehponline

Preowned Problems: PBDEs in Discarded Furniture

Furniture industry experts expect furnishings free of flame retardants to become increasingly popular with consumers who can afford it, and people who purchase these items may reduce their exposures to certain chemicals. But what happens to older furniture that enters the waste stream?

Diversity Outbred: A New Generation of Mouse Model

Most mice used in toxicology research are genetically inbred and thus genetically identical, making it tricky to predict how the findings relate to the genetically diverse human population. A new genetically diverse mouse model, known as Diversity Outbred, offers intriguing possibilities for toxicology research.

Featured research and related news articles this month include:

- **Air Pollution and ASDs: Homing In on Environmental Risk Factors** — Researchers used data from 1,767 women in the Nurses' Health Study II to study particulate matter pollution as a potential environmental risk factor that could contribute to autism spectrum disorders.

- **Comparing Models: DBP Effects in Rat and Human Germ Cells** — A new study more narrowly defines di(n-butyl) phthalate's effects on germ cells and establishes that a rat model is suitable for clarifying how DBP affects some aspects of human germ cells.

- **Roadmap for Children's Health: Controlling Diverse Environmental Exposures in Latin America** — Participants of a 2012 World Health Organization and Pan American Health Organization conference review the health dangers of environmental pollutants for children who live in Latin America.

- **Continental Reference Point: Harmonized Human Biomonitoring Across Europe** — Researchers report on a human biomonitoring project that surveyed levels of mercury, cadmium, and metabolites of nicotine and phthalates in residents of 17 European nations.

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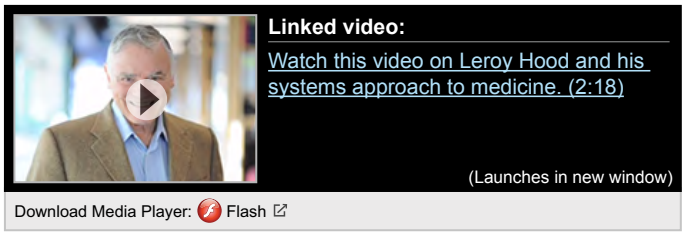
Systems biology pioneer Leroy Hood to give Rodbell Lecture

By Eddy Ball

NIEHS will welcome Leroy Hood, M.D., Ph.D., to present the annual Dr. Martin Rodbell Lecture, March 10 at 11:00 a.m., in NIEHS Rodbell Auditorium. Hood will explore "Systems Medicine and Proactive P4 Medicine: Catalyzing a Revolution in Healthcare."

Hood is founder and president of the Institute for Systems Biology (ISB), a nonprofit biomedical research organization based in Seattle. One of the central concepts at ISB is a predictive, personalized, preventive, and participatory approach to medicine, or P4 medicine. "It [P4 medicine] will represent a network of networks — genetic networks, molecular networks, cellular networks, tissue networks, individual networks, population networks, and social networks," Hood has said.



Hood joins some of the country's leading scientists, several of them Nobel laureates, who have presented Rodbell Lectures at NIEHS. (Photo courtesy of ISB)

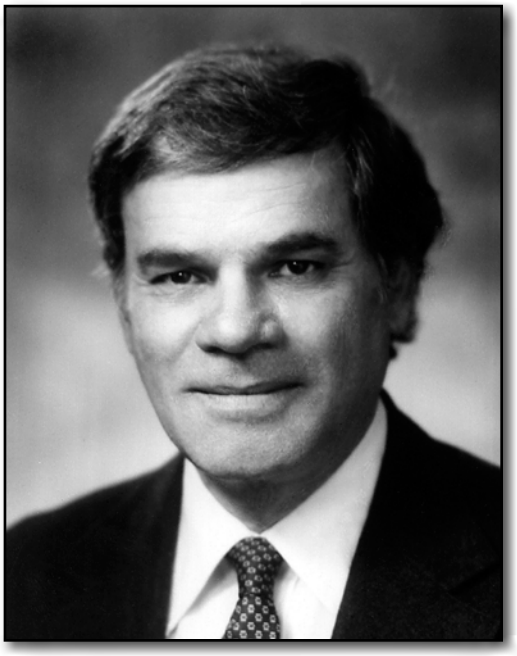
"We are very fortunate to have a scientist, inventor, and entrepreneur of Dr. Hood's caliber speaking at NIEHS," said Kristine Witt, National Toxicology Program (NTP) Genetic Toxicology Group leader. "I'm sure scientists across the institute will be eager to hear his talk." Witt and Warren Casey, Ph.D., director of the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods, will co-host Hood's talk.

A record of excellence

Prior to founding ISB in 2000, Hood served as chairman and founder of the Department of Molecular Biotechnology at the University of Washington; chair of the Division of Biology at the California Institute of Technology, where he completed his Ph.D. in 1968; and a senior scientist at the National Cancer Institute. Hood earned his M.D. at Johns Hopkins University in 1964.

Hood has published more than 750 peer-reviewed papers, been granted 36 patents, received 17 honorary degrees, and founded or co-founded 15 different biotechnology companies, including Amgen, Applied Biosystems, Rosetta, Darwin, Integrated Diagnostics, and Indi Molecular. In recognition of his scientific discoveries and engineering advances, Hood has received more than 100 awards and honors, including some of the highest honors in his fields of endeavor.

The Rodbell Lecture is one of two named talks in the annual NIEHS Distinguished Lecture Series. It honors former NIEHS Scientific Director and Nobel laureate Martin Rodbell, Ph.D. Rodbell shared the 1994 Nobel Prize in physiology or medicine with Alfred Gilman, Ph.D., for the discovery of G-proteins, signal transducers that transmit and modulate signals in cells to control fundamental life processes.



Rodbell presented the first talk in the series shortly before his death in 1998. (Archive photo courtesy of Steve McCaw)

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RTI announces upcoming metabolomics opportunities

By Eddy Ball

In an invitation to scientists at NIEHS, the metabolomics research center at RTI International announced its spring meeting and an upcoming international conference, along with the approaching deadline for metabolomics grant applications.

Grant applications being accepted

The National Institutes of Health (NIH) Eastern Regional Comprehensive Metabolomics Research Center (RCMRC) at RTI will accept applications for pilot and feasibility studies up to its deadline of Mar. 16.

Information on proposal applications can be downloaded from the RTI RCMRC website. Applicants are encouraged to discuss their proposals with the RTI RCMRC Director Susan Sumner, Ph.D., at ssumner@rti.org or 919-541-7479); or Program Coordinator Jason Burgess, Ph.D., at jpb@rti.org or 919-541-6700.

Upcoming metabolomics meetings

RTI will host its NIH Eastern RCMRC spring symposium Mar. 27 9:00 a.m.-4:30 p.m. in its Dreyfus Auditorium on the RTI campus, 3040 East Cornwallis Road, in Research Triangle Park, North Carolina. Cosponsoring the event is the LECO Corporation, which specializes in analytical instrumentation research and development.

The event is free and includes a complimentary lunch, but registration is required.

Sumner will discuss "Opportunities for Pilot and Feasibility Studies with the RTI RCMRC: Proof of Concept for Large Scale Studies."

Other presenters include Krista Zanetti, Ph.D., of the National Cancer Institute; Oliver Fiehn, Ph.D., of the West Coast Metabolomics Center at the University of California, Davis; Mark Styczynski, Ph.D., Georgia Institute of Technology; Eric Johnson, Ph.D., RTI; and Laura Schnackenberg, Ph.D., of the U.S. Food and Drug Administration.

RTI also announced the 11th International Conference of the Metabolomics Society June 29-July 2 in San Francisco. Abstracts may be submitted through Mar. 15. Registration will close May 30.

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Extramural papers of the month

By Nancy Lamontagne

- Prenatal BPA exposure linked with higher levels of oxidative damage
- Vitamin B protects against DDT-associated fertility problems
- BPA may be especially harmful to heart health of females
- People and mice share epigenetic differences tied to obesity

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

Prenatal BPA exposure linked with higher levels of oxidative damage

NIEHS grantees report that exposure during pregnancy to the endocrine-disrupting chemical bisphenol A (BPA) can cause oxidative damage that may increase the child's risk of developing diabetes or heart disease later in life. The researchers tested multiple species of animals to replicate and strengthen human studies showing BPA exposure during pregnancy can bring about a specific type of oxidative stress.

Oxidative stress is associated with insulin resistance and inflammation, which are risk factors for diabetes and other metabolic disorders, as well as cardiovascular disease. For the human study, the researchers analyzed blood samples from 24 mother and infant pairs. The women were divided into two groups based on levels of BPA, determined from blood draws taken during the first trimester of pregnancy. Mothers and their infants with higher levels of BPA showed increased levels of a marker of nitrosative stress, known as 3-nitrotyrosine. Nitrosative stress is a type of oxidative stress brought about by the free radical nitric oxide or reactive species derived from it. For the animal studies, the researchers examined the effects of BPA on sheep, rats, and mice by prenatally treating the animals with BPA at doses similar to what people would experience. The animals showed increased systemic nitrosative stress, which indicates a causal link between BPA exposure and this type of oxidative stress.

Overall, the findings demonstrate an association between increased BPA exposure and increased systemic nitrosative stress. The results also support the potential use of maternal 3-nitrotyrosine as a health status biomarker for future offspring.

Citation: Veiga-Lopez A, Pennathur S, Kannan K, Patisaul HB, Dolinoy DC, Zeng L, Padmanabhan V. 2015. Impact of gestational bisphenol A on oxidative stress and free fatty acids: human association and interspecies animal testing studies. Endocrinology 156(3):911-922.

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Vitamin B protects against DDT-associated fertility problems

New research, supported in part by NIEHS, shows that B vitamins can help protect against increased risk of miscarriage, which is associated with high levels of 1,1,1-trichloro-2,2,bis(p-chlorophenyl)ethane (DDT) in the body.

From 1996 to 1998, the researchers followed female Chinese textile workers who were trying to get pregnant. They measured preconception concentrations of vitamin B-6, vitamin B-12, and folate in blood plasma, as well as serum total DDT. Among the 291 women in the study, there were 385 conceptions, of which 31 percent were lost before six weeks. The time to conception was longer and the frequency of pregnancy was lower in women with B-vitamin deficiency and high DDT blood levels, than in women with adequate B-vitamin levels and low DDT. For the women with high DDT, conception frequency increased by 47 percent for every 17.8 nanomoles per liter increase in vitamin B-6, and the likelihood of an early pregnancy loss was reduced by 45 percent with every 4.8 nanomoles per liter increase in folate.

Researchers suggest that higher preconception intake of B vitamins, through fortified foods and improved nutrition, could help improve pregnancy outcomes in countries where DDT is still used.

Citation: Ouyang F, Longnecker MP, Venners SA, Johnson S, Korrick S, Zhang J, Xu X, Christian P, Wang MC, Wang X. 2014. Preconception serum 1,1,1-trichloro-2,2,bis(p-chlorophenyl)ethane and B-vitamin status: independent and joint effects on women's reproductive outcomes. Am J Clin Nutr 100(6):1470-1478.

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BPA may be especially harmful to heart health of females

An NIEHS grantee and colleagues report that exposure to the endocrine disruptor bisphenol A (BPA) from birth though young adulthood affects the heart function and blood pressure of male mice differently from that of female mice. The results add more evidence that BPA can adversely affect the cardiovascular system and suggest that females are particularly sensitive to heart damage from BPA.

The researchers fed mice with food containing various amounts of BPA, which resulted in exposures ranging from 4 to 5,000 micrograms per kilogram of body weight per day. They observed changes in the control of heart rate and blood pressure in both male and female BPA-exposed mice. Male mice exposed to BPA above 5 micrograms and female mice exposed to the highest amounts of BPA showed decreased systolic blood pressure.

To mimic some of the effects of a heart attack, the researchers administered isoproterenol, a drug that leads to tissue enlargement. In BPA-exposed female mice, isoproterenol caused increased heart muscle damage along with accumulation of collagen, which indicates fibrosis or scarring. In male mice, BPA exposure without isoproterenol increased fibrosis, but isoproterenol treatments didn't cause any additional increase in fibrosis, ischemic damage, or hypertrophy. The researchers also conducted a RNA sequence analysis, which identified significant sex-specific changes in gene expression in mice exposed to BPA.

Citation: Belcher SM, Gear R, Kendig EL. 2015. Bisphenol A alters autonomic tone and extracellular matrix structure and induces sex-specific effects on cardiovascular function in male and female CD-1 mice. Endocrinology 156(3):882-895.

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People and mice share epigenetic differences tied to obesity

Research, supported in part by NIEHS, found a surprising similarity between obesity-induced epigenetic marks in mice and humans. These findings might provide new routes to prevent and study obesity, as well as insight into how the environment might bring about epigenetic changes that can lead to obesity-related diseases, such as type 2 diabetes.

Epigenetic marks are chemical modifications, such as the addition of a methyl group, that change how DNA is expressed without changing the genetic code. The researchers analyzed more than 7 million sites in the DNA of fat cells in lean and obese mice and found clear differences in methylation patterns. They also looked at changes in DNA methylation in people before and after gastric bypass surgery. Of the 625 regions of DNA with methylation patterns associated with obesity in the mice, 249 regions showed significant conserved methylation changes associated with obesity in people.

The researchers used genetic association data from a large type 2 diabetes genome-wide association study to link their findings with disease. This revealed that some of the obesity-associated methylation patterns affected genes known to raise diabetes risk, while others affected genes that had not been conclusively linked to the disease but did have roles in metabolism. It also identified some DNA regions that might be susceptible to environmental factors that influence methylation.

Citation: Multhaup ML, Seldin MM, Jaffe AE, Lei X, Kirchner H, Mondal P, Li Y, Rodriguez V, Drong A, Hussain M, Lindgren C, McCarthy M, Naslund E, Zierath JR, Wong GW, Feinberg AP. 2015. Mouse-human experimental epigenetic analysis unmasks dietary targets and genetic liability for diabetic phenotypes. Cell Metab. 21(1):138-149.

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

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Intramural papers of the month

By Tara Ann Cartwright, Deacqunita Diggs, Geoffrey Feld, Vijay More, and Qing Xu

- NTP finds that indium-induced pulmonary toxicity depends on particle solubilization
- Ctp1 acts as a bridge over troubled DNA
- Genome-wide p53 binding is independent of chromatin state, but response depends on it
- The role of the NLRP3 inflammasome in obesity resistance and insulin sensitivity of NAG-1 mice
- Testosterone and peritubular myoid cells involved in maintenance of spermatogonial stem cell microenvironment

NTP finds that indium-induced pulmonary toxicity depends on particle solubilization

While studying indium phosphide and indium-tin oxide-induced pulmonary toxicity, researchers from the National Toxicology Program revealed that the lung toxicity of these compounds was dependent upon particle solubilization, not total indium content. The research found that particle solubilization and cytotoxicity data, generated *in vitro* with macrophages, accurately predicted pulmonary toxicity *in vivo*. Since indium-containing particles are widely used in the semiconductor and microelectronics industries, the work has a bearing on occupational health.

Macrophage solubilization of particles and cytotoxicity *in vitro* correlated positively with findings from *in vivo* studies in which mice were exposed to indium phosphide or indium-tin oxide via oropharyngeal aspiration. Owing to greater particle solubilization by macrophages, cytotoxicity, and hence greater release of the toxic constituent, ionic indium, indium phosphide was far more toxic than indium-tin oxide, both *in vitro* and *in vivo*. The authors propose an *in vitro* model that can be used for toxicity predictions for indium-containing particles and possibly other metal-containing particles, potentially leading to reduced use of animals for pulmonary toxicity testing. **(VM)**

Citation: Gwinn WM, Qu W, Bousquet RW, Price H, Shines CJ, Taylor GJ, Waalkes MP, Morgan DL. 2014. Macrophage solubilization and cytotoxicity of indium-containing particles as in vitro correlates to pulmonary toxicity in vivo. Toxicol Sci; doi:10.1093/toxsci/kfu273 [Online 19 December 2014].

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Ctp1 acts as a bridge over troubled DNA

Using X-ray crystallography, biophysical techniques, and yeast genetics, NIEHS scientists revealed that Ctp1/CtIP/Sae2, a critical protein involved in the eukaryotic DNA damage response, binds and bridges DNA. The discovery illuminates a new function for the protein. Ctp1 family proteins coordinate with the Mre11/Rad50/Nbs1 nuclease complex, a central component of DNA double-strand break (DSB) repair machinery. Mutations in CtIP, the human homologue of Ctp1, are linked to Seckel and Jawad syndromes, two genetic diseases characterized by microcephaly and dwarfism.

In describing Ctp1molecular architecture, the authors identified three key regions with interconnected functionality. First, they determined the crystal structure of a conserved N-terminal tetrameric helical dimer-of-dimers domain (THDD) that enables Ctp1 to form a functional tetramer. Next, they demonstrated that both the THDD and a conserved C-terminal CxxC-RHR motif (RHR) possess DNA binding properties with preference for forked DNA, and that Ctp1 can bind two separate DNA molecules simultaneously. Finally, a flexible, intrinsically disordered region containing multiple DSB-responding protein-binding motifs separates the THDD and RHR. Thus, Ctp1 is a flexible multivalent DNA binding protein capable of recruiting repair partners to and bridging the broken stands of a DSB.

The ability of Ctp1 to bind DNA is paramount to its repair function *in vitro* and *in vivo* to protect cells from endogenous and environmental DNA damage. For example, yeast strains lacking Ctp1 DNA binding capacity show DNA repair deficiencies, and are sensitive to genotoxic insult. Future studies into the DNA binding properties of Ctp1/CtIP may provide a molecular basis for CtIP-linked diseases, opening the door for future therapeutics. **(GF)**

Citation: Andres SN, Appel CD, Westmoreland JW, Williams JS, NguyenY, Robertson PD, Resnick MA, Williams RS. 2015. Tetrameric Ctp1 coordinates DNA binding and DNA bridging in DNA double-strand-break repair. Nat Struct Mol Biol 22(2):158-166. [Story]

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Genome-wide p53 binding is independent of chromatin state, but response depends on it

Researchers from NIEHS and Duke University have characterized binding of p53 response elements (p53REs) and the corresponding chromatin landscape across the whole genome, in a cell model exposed to a chemotherapeutic drug. The findings provide new knowledge for developing approaches to prevent or treat cancer.

Tumor suppressor p53 is well known for its role in carcinogenesis. When activated by DNA damage, p53 binds to its DNA response elements and regulates transcription of genes involved in DNA repair and cell death.

In this study, the researchers analyzed stress-induced changes of p53 binding, chromatin state, and gene expression, after treating human lymphoblastoid cells with the DNA-damaging agent doxorubicin, and then mapped p53 binding and the chromatin activation mark, H3K4me3, by ChIP-seq. They discovered that p53-responsive genes showing the largest changes in expression had low levels of H3K4me3 and were repressed at baseline. Binding sites with greater similarity to p53RE consensus sequence correlated with increased p53 occupancy. However, the chromatin landscape strongly influenced the relationship between occupancy and gene induction.

Surprisingly, p53 strongly bound to thousands of DNA elements located in repressed chromatin that have recently evolved from human retroviral transposons. Characterizing the chromatin-mediated p53 stress response and the deregulation of transposons may prove to be clinically relevant for understanding outcomes in cytotoxic therapy for cancer. **(QX)**

Citation: Su D, Wang X, Campbell MR, Song L, Safi A, Crawford GE, Bell DA. 2015. Interactions of chromatin context, binding site sequence content, and sequence evolution in stress-induced p53 occupancy and transactivation. PLoS Genet 11(1):e1004885.

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The role of the NLRP3 inflammasome in obesity resistance and insulin sensitivity of NAG-1 mice

Researchers from NIEHS have conducted the first study to characterize the association of the NLRP3 inflammasome with diet-induced obesity and improved insulin sensitivity in NSAID activated gene-1 (NAG-1) transgenic mice. The NLRP3 inflammasome is a multiprotein complex that activates caspase-1, leading to the secretion of the proinflammatory cytokines Interleukin (IL)-1beta and IL-18. Both IL-1beta and IL-18 have been associated with obesity, insulin resistance, and type 2 diabetes.

The study demonstrated that, compared with their wild-type littermates, NAG-1 Tg mice, whether fed with a low fat or high fat diet, had lower NLRP3 inflammasome activity and lower expression of NLRP3 proteins,

caspase-1, and apoptosis-associated speck-like protein. Expression of IL-1beta, IL-18, and TNFalpha in white adipose tissue (WAT) was also reduced. Furthermore, NAG-1 Tg mice exhibited significantly lower levels of leptin, more insulin sensitivity, and reduced mRNA levels of macrophage infiltration markers F4/80, CD11b, and CD11c in WAT.

Taken together, this study suggests that NAG-1 may be an important regulator in the development of obesity. The mechanism by which NAG-1 plays a protective role in obesity appears, in part, to be mediated by changes in NLRP3 inflammasome activity. **(TAC)**

Citation: Wang X, Chrysovergis K, Kosak J, Eling TE. 2014. Lower NLRP3 inflammasome activity in NAG-1 transgenic mice is linked to a resistance to obesity and increased insulin sensitivity. Obesity (Silver Spring) 22(5):1256-1263.

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Testosterone and peritubular myoid cells involved in maintenance of spermatogonial stem cell microenvironment

NIEHS scientists suggest that testosterone-dependent regulation of glial cell line-derived neurotrophic factor (GDNF) in peritubular myoid (PM) cells influences spermatogonial stem cell (SSC) maintenance *in vitro*. GDNF is a protein that is involved in the maintenance, proliferation, and self-renewal of SSCs, and is produced by PM cells *in vitro*. Since conditions in the microenvironment determine whether SSCs undergo self-renewal or differentiation, this work may provide a better understanding of how male mice sustain sperm production throughout their reproductive years.

PM cells and Sertoli cells form the cellular boundary of the SSC microenvironment, but scientists did not know what role PM cells played in SSC maintenance. The researchers employed an adult mouse PM cell primary culture system and germ cell transplantation to find out. They determined that testosterone induced GDNF expression in PM cells. They also cocultured PM cells, with and without testosterone, and thymocyte antigen 1-positive spermatogonia. When the cells were transplanted to the testes of germ cell-depleted mice, the SSCs cocultured with testosterone-treated PM cells rendered significantly more transplant-derived colonies.

This research confirms other studies that assert GDNF is necessary for the ability of SSCs to undergo proliferation and self-renewal *in vitro*, but it also supports the hypothesis that PM cells exert a heavy influence on SSC maintenance. **(DD)**

Citation: Chen LY, Brown PR, Willis WB, Eddy EM. 2014. Peritubular myoid cells participate in male mouse spermatogonial stem cell maintenance. Endocrinology 155(12):4964-4974.

(Tara Ann Cartwright, Ph.D., is a former postdoctoral fellow in the NIEHS Intracellular Regulation Group. Deacqunita Diggs, Ph.D., is a National Health and Environmental Effects Laboratory fellow in the EPA Developmental Toxicity Branch. Geoffrey Feld, Ph.D., is an Intramural Research Training Award fellow in the NIEHS Genome Stability Structural Biology Group. Vijay More, Ph.D., is a visiting fellow in the NIEHS Intracellular Regulation Group. Qing Xu is a biologist in the NIEHS Metabolism, Genes, and Environment Group.)

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Inside the Institute

NIEHS scientists reflect on the legacy of Tuskegee during Black History Month

By Eddy Ball

This February, graduates of the Tuskegee University School of Veterinary Medicine paused to share memories of their alma mater during Black History Month at NIEHS.

Toxicologic pathologists Darlene Dixon, D.V.M., Ph.D.; Ronald Herbert, D.V.M., Ph.D.; and Robert Sills, D.V.M., Ph.D.; and laboratory animal medicine specialist Angela King-Herbert, D.V.M., all got their start in advanced biomedical research in veterinary medicine at Tuskegee during the 1980s, before continuing their educations at other leading universities, including Michigan State University, Purdue University, and North Carolina State University.

All are group leaders in the National Toxicology Program (NTP), headquartered at NIEHS. In addition, Sills is chief of the Cellular and Molecular Pathology Branch in the Division of NTP. They have all been recognized in their fields for leadership and research, as well as for their spirit of service.

"Their scientific accomplishments at the National Institutes of Health [NIH] are certainly many," said Gerard Roman of the NIH Office of Equity, Diversity, and Inclusion. "But every year, these scientists are also engaged in some way to support science education and mentoring, and promote diversity and inclusion."

Remembering the personal legacy of an education at Tuskegee

As the alumni talked about their years at the university, it became clear that Tuskegee was a special place for them in a number of ways. It represented a cultural contrast to their experiences growing up in major urban centers, it was a place where they were more than just another number, and it fostered the kind of atmosphere where the young scientists felt nurtured, as well as individually challenged, by their mentors and role models.

"They were sometimes hard on us," said Dixon, who turned down offers from Rutgers University and St. Bonaventure University to come to Tuskegee. "But it was done so we would be better." (Photo courtesy of Steve McCaw)

"They [the faculty] were always pushing you to do your best," Herbert said. He said his grades, which were good at City College, improved even more because of the supportive environment at Tuskegee. (Photo courtesy of Steve McCaw)

"Everybody was so welcoming," said Dixon, who came south after completing high school in New Jersey and turning down offers from schools in the north. "There were people there who were committed to lifting up other people, committed to giving us the opportunity to really reach our full potential," she added. "When I saw that happening for me there, I knew I wanted to do the same thing."

Like Dixon, King-Herbert credits networking with other students, including those in the veterinary program, as well as colleagues and professors in several disciplines in the sciences and humanities, with helping to motivate her to apply for and receive early admission to the veterinary program during her junior year at Tuskegee.

"That was the foundation for me wanting to help others, because I knew how the professors helped me when they knew my desires and my goals," King-Herbert said, pointing also to the university's Minority Biomedical Support Program.

Outreach by King-Herbert and other Tuskegee alumni is one of the reasons graduates of the program there have a phenomenally high rate of passing the certification examination in laboratory animal medicine. (Photo courtesy of Steve McCaw)

In addition to his long service with NTP, Sills has developed academic and mentoring ties to Michigan State University, where he earned his doctorate in pathology after completing the veterinary program at Tuskegee. (Photo courtesy of Steve McCaw)

Marking 70 years of veterinary medical education

Tuskegee has been a leader in the education of African-American students for nearly 135 years as one of the top historically black universities or colleges (HBUC) in the country. Its School of Veterinary Medicine is the only fully accredited doctoral degree-granting program in veterinary medicine at an HBUC. Tuskegee produces more that 75 percent of the African-American veterinarians in the world, including nearly 92 percent of veterinarians from other countries who have studied in the U.S. for this professional degree.

The veterinary school is made up three departments — Biomedical Sciences, Clinical Sciences, and Pathobiology — as well as a state-of-the-art Veterinary Teaching Hospital. Established in 1945, the school granted its first doctorate in 1948 and has been accredited by the Council on Education of the American Veterinary Medical Association since 1949.

Last year Donald Smith, D.V.M., wrote "A Tribute to Tuskegee," which highlights the school's contributions to veterinary medicine worldwide, and other "Stories of African-American Veterinary History." Smith is the Austin O. Hooey Dean Emeritus of Veterinary Medicine and emeritus professor of surgery at Cornell University.

For Herbert, the road to Tuskegee led from his native Barbados to his first year of college at the City College of New York, and then to Alabama. When he arrived on campus, he soon found himself in a different place. “It’s one big family, and the faculty really care,” he said. “They were always trying to help,” even when it came to money problems.

Today, the Tuskegee alumni at NIEHS have worked as veterinary specialists for more than 20 years, and their professional accomplishments include prestigious certifications, honors, and leadership roles in professional organizations.

Behind the scenes, however, is something that their curricula vitae do not reflect as clearly — the hundreds of young scientists, students, trainees, and colleagues at NIEHS and elsewhere who have benefited from the powerful Tuskegee legacy of giving back.

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National Institute of Environmental Health Sciences

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