

February 2014

NIEHS Spotlight



[NIEHS exposome faculty connects scientists from across the institute](#) ▶ Audio

Scientists from all corners of the institute meet in January to explore what studying the exposome can mean at NIEHS.



[Research supported by NIEHS informs policy and regulatory discussion](#)

NIEHS-funded researchers found themselves, this winter, at center stage in the national discussion concerning public health policy and regulatory issues.



[International collaboration aims to reduce animal testing](#) ▶ Video

The NTP alternative methods program met with international partners Nov. 26-27 in Italy to reach important agreements for advancing 21st century safety testing.



[Harvard SRP collaboration honored for risk communication](#)

The Kids + Chemical Safety website receives Risk Communication award for providing parents with peer-reviewed information on chemical risks to children.



[NTP scientists achieve coveted toxicology certification](#)

This winter, two NTP contract scientists and two NTP postdoctoral fellows received Diplomate of the American Board of Toxicology certification.

Science Notebook



[Using nanomedicine to improve human health](#) ▶ Video

Materials scientist Joseph DeSimone, Ph.D., explored the use of nanoparticles to design better medicines and vaccines in an NIEHS Distinguished Lecture Jan. 24.



[New NTP atlas helps standardize nonneoplastic lesion diagnoses](#)

In January, NTP debuted a new web-based resource that will help pathologists worldwide better diagnose, record, discuss, and discriminate among rodent lesions.



[Scientists begin to fill in the gaps in understanding about fracking](#) ▶ Video

New studies by NIEHS-funded researchers are helping raise awareness of the potential environmental public health impact of this unconventional natural gas drilling method.



[Community engagement drives new pilot study on fracking and air quality](#) ▶ Audio

A team of NIEHS-funded researchers met Jan. 9 with citizens of Carroll County, Ohio, marking one of the first steps in the one-year project.



[Wastewater treatment offers a view into environmental chemicals' risks](#)

Arizona State University researchers analyzed biosolids from municipal wastewater treatment plants to identify contaminants of emerging concern.

NIEHS Spotlight



[Grantees named AAAS fellows](#)

Four NIEHS grantees will be among new fellows honored this year by the American Association for the Advancement of Science at its annual meeting in Chicago.



[NIEHS fellow begins career in educational writing](#)

In December, former NIEHS fellow Jacqueline de Marchena Powell, Ph.D., translated her postdoc experience into a career as a science writer.



[Postdoc transitions into career in biopharmaceuticals](#)

After three years at NIEHS, Jeremy Weaver, Ph.D., found his perfect match with a position as a process development scientist at Grifols Therapeutics Inc.



[2014 calendar features artwork by NIEHS postdoc](#)

This September, artwork by Sheila Yong, Ph.D., will be on display in offices, labs, and cubicles around the world, as part of Abcam's new desk calendar.



[Biostatistics intern reaches national semifinals for science competition](#)

NIEHS summer intern Mitás Ray was named semifinalist in the Intel Science Talent Search, earning awards for himself and his school, Enloe High School in Raleigh, N.C.

Science Notebook



[High-throughput screening examines multiple effects of 1060 compounds on zebrafish](#)

Large systematic *in vivo* toxicological study finds nearly half the chemicals tested show significant biological responses and detects responses other methods would miss.



[Study identifies novel compounds more mutagenic than parent PAHs](#)

SRP researchers discover novel nitrated-PAHs that form under normal combustion conditions and have greater mutagenic properties.



[Using teeth to uncover developmental susceptibility to chemical mixtures](#) ▶ Audio

Children's baby teeth can reveal prenatal and early childhood exposures to a variety of chemicals — data useful for researching health impacts in later life.



[Webinar highlights new insights about childhood leukemia](#)

In a webcast seminar Jan. 8, two NIEHS-funded scientists from the University of California, Berkeley presented new findings about childhood leukemia.



[Talk explores link between endometriosis and the estrogen receptor](#)

A meeting of the NIEHS Receptor Mechanisms Discussion Group Jan. 7 featured a seminar by postdoctoral fellow Katherine Burns, Ph.D.

Inside the Institute



[NIEHS CFC raises more than \\$100,000](#)

Led by DERT co-chairs, employees respond with enthusiastic support for more than 300 organizations that deliver services to those in need.



[NIEHS inaugurates new facilities for fitness, research, and training](#)

Birnbaum and staff celebrate newly remodeled main building facilities at Jan. 8 open house.

Science Notebook



[This month in EHP](#)

The February issue of Environmental Health Perspectives (EHP) highlights health effects on the Navajo population of earlier uranium mining, and radioactive consequences of fracking.



[Myles Brown to give distinguished lecture](#)

The second NIEHS distinguished lecture of 2014 will be presented Feb. 11 by prominent physician scientist Myles Brown, M.D., at 11:00 a.m. in Rodbell Auditorium.

Extramural Research

[Extramural papers of the month](#)

- [Transcription factor influences codon choice and protein evolution](#)
- [Compound from mold linked to symptoms of Parkinson's disease](#)
- [New tool for assessing ovarian cancer](#)
- [Partnership identifies chemical-gene-disease interactions for inclusion in database](#)

Intramural Research

[Intramural papers of the month](#)

- [Scientists closer to understanding stem cell self-renewal and differentiation](#)
- [Estrogen receptor alpha involved in DES-induced gene expression in male mice](#)
- [Identification of a novel mechanism that suppresses glucocorticoid signaling](#)
- [Factors critical during early stages of heart development clarified](#)

Calendar of Upcoming Events

- **Feb. 5**, in Rodbell Auditorium, 8:30 a.m.-5:00 p.m. — Bisphenol A Grantee Meeting
- **Feb. 6**, in Rodbell Auditorium, 9:00-10:00 a.m. — Keystone Science Lecture Seminar Series with Carl White, Ph.D., addressing “Novel Countermeasures Against Chemically Induced Airways Injury”
- **Feb. 7**, in Rodbell Auditorium, 11:00 a.m.-noon — African American History Month with Crystal deGregory, Ph.D., speaking on “Herstory: Civil Rights (and Wrongs) at Home and Abroad”
- **Feb. 11**, in Rodbell Auditorium, 11:00 a.m.-noon — Distinguished Lecture Series presentation on “Genetics and Epigenetics of Hormone Dependence” by Myles Brown, M.D.
- **Feb. 12-13**, in Rodbell Auditorium; Feb. 12, 8:30 a.m.-5:30 p.m., Feb. 13, 8:30 a.m.-1:00 p.m. — Transgenerational Inheritance in Mammals after Environmental Exposure Grantee Meeting
- **Feb. 13**, in Rodbell Auditorium, 1:00-2:00 p.m. — Keystone Science Lecture Seminar Series with Andrea Gore, Ph.D., discussing “Environmental Endocrine Disruption of the Brain: Past, Present, and Future”
- **Feb. 13 (offsite event)**, in the Trent Center for Bioethics, Humanities, and History of Medicine, Room 40, Duke University, noon-1:00 p.m. — Richard Kwok, Ph.D., discussing “The Gulf Study: Investigating the Human Health Effects of the BP Deepwater Horizon Oil Spill”
- **Feb. 14 (offsite event)**, in the Levine Science Research Center, Room 247, Duke University, noon-1:00 p.m. — Integrated Toxicology and Environmental Health Program Spring 2014 Seminar Series, featuring Daniel Baden, Ph.D., exploring “From Beach to Bedside: Getting our Feet Wet in Translational Marine Science”
- **Feb. 19-20**, in Rodbell Auditorium; Feb. 19, 8:30 a.m.-5:30 p.m., Feb. 20, 8:30a.m.-2:00 p.m. — National Advisory Environmental Health Sciences Council
- **Feb. 20**, in Rodbell Auditorium, 2:00-5:00 p.m. — Launch of NIEHS-WHO Collaborating Center
- View More Events: [NIEHS Public Calendar](#)

NIEHS Spotlight

NIEHS exposome faculty connects scientists from across the institute

By Kelly Lenox

Scientists from across NIEHS gathered Jan. 10 to help inaugurate the Institute's exposome faculty. This was the second meeting of the newly formed group, which is working to develop the concept and study of exposome science at NIEHS.

The exposome, or the measure of a person's lifelong exposures to agents, both internal and external, is attracting increased attention from environmental health scientists worldwide.

Creation of the exposome faculty supports Goal 3 of the NIEHS [2012-2017 Strategic Plan](#), which calls for transforming exposure science by enabling consideration of the totality of human exposures and incorporating exposure science into human health studies. Priorities identified under the goal include defining and disseminating the concept of the exposome, and creating the tools and technologies, as well as research capacity, needed to characterize the exposome.

Grappling with definitions

Definitions of the exposome have varied since Christopher Wild, Ph.D., a cancer epidemiologist, first coined the word in a [2005 journal article](#). According to David Balshaw, Ph.D., acting chief of the NIEHS [Exposure, Response, and Technology Branch](#) and Exposure Biology Research Program lead, the scientific community is looking to NIEHS for leadership as a primary deliberative body for defining the emerging field of the exposome and exposomics.

Balshaw reminded participants not to overlook the rationale behind studying the exposome. Wild's initial definition of the exposome as the totality of life-course exposures from the prenatal period onwards is a grand vision and technically daunting.

"Definitions can be divisive. The essence of the exposome is that it will allow us to identify the associations between exposure and disease without preformed hypotheses," said Balshaw. "Rather than asking what is the association between particulate matter exposures and asthma, we can ask the broader question of what are the environmental factors that determine this biological endpoint. The science of the exposome is in how you perform that analysis."



Longnecker offered examples of how current epidemiological studies might differ from exposome studies. "For instance, [one study] used dust samples, but not air samples," he said. (Photo courtesy Steve McCaw)



Balshaw described the exposome as a means of discovering associations between environmental exposures and a biological point of interest. (Photo courtesy Steve McCaw)

Obtaining, storing, and processing data gets expensive

Matthew Longnecker, M.D., Sc.D., head of the NIEHS [Biomarker-based Epidemiology Group](#), discussed three cohort studies currently underway — the [Sister Study](#), the [GuLF STUDY](#), and the [Norwegian Mother and Child Cohort Study](#) — and described how data requirements for exposome studies might differ from the needs of the studies.

“In some cases, the data so far represent one point in time. Data and sample size are often limited by the expense of collecting and storing samples, as well as data processing,” he said.

Monitoring external and internal exposures

Next, Balshaw described activities of the Gene, Environment, and Health Initiative Exposure Biology Program, funded from 2007-2011 to explore whether exposure could be measured in a new manner. The program focused on developing tools for exposure assessment in the personal environment, including monitors for external exposure, using stress metrics and information on abuse of substances, and measuring biological responses.

Involving communities in data collection

The third speaker, Liam O’Fallon of the NIEHS [Partnerships for Environmental Public Health \(PEPH\)](#) program, reported on community engagement activities to explore how the exposome relates to public health work. O’Fallon pointed to one example of how communities can be involved in collecting the necessarily extensive data.

“The Environmental Health Sciences Core Center at Emory University is working with community partners who understand the utility of the exposome,” he explained.

As part of the [Environmental Health Chat](#) series, PEPH recently released a podcast that explains the concept of the exposome and how it can help community organizations address their environmental health concerns.

 [Listen as Gary Miller, Ph.D., of Emory University, and others describe how understanding the exposome can help protect people at a societal level \(06:43\).](#)

 [Read Transcript](#)

Coming soon: workshop and webinars

The exposome faculty’s role ranges from providing a forum to discuss and define the exposome concept, to fostering collaborations across NIEHS related to the exposome. Furthermore, plans call for a bimonthly webinar series to begin soon, as well as a workshop later in the year.

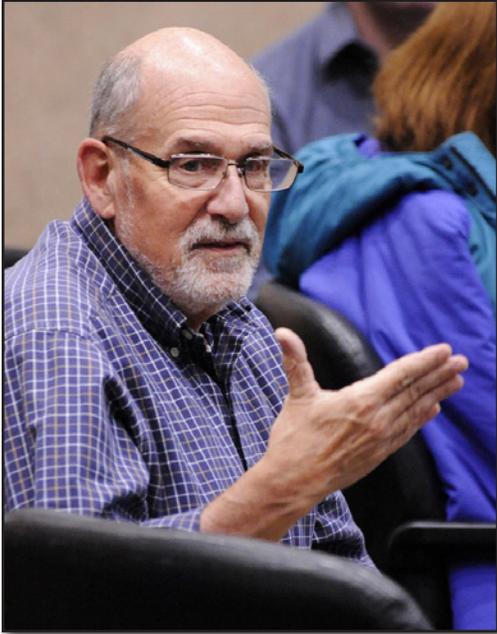


“Many different organizations have observed that there are multiple exposures they have to deal with, but to them it seems scientists look at one exposure and one health outcome,” said PEPH program lead O’Fallon. “That isn’t reflective of their realities. The exposome is an opportunity to more realistically examine environmental justice and environmental health disparities.” (Photo courtesy Steve McCaw)



Richard Kwok, Ph.D., is the lead associate investigator for the GuLF STUDY, mentioned during Longnecker’s discussion on exposure data. (Photo courtesy Steve McCaw)

Balshaw summed up the role by saying, “The exposome faculty is first and foremost a forum to talk about what the exposome is and what we as an Institute should be doing.”



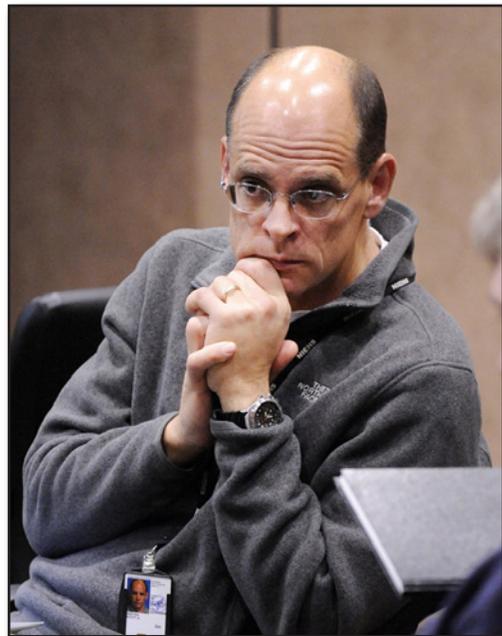
The work of David Miller, Ph.D., chief of the Toxicology and Pharmacology Laboratory, includes understanding how blood-brain barrier transport function is altered by environmental stressors and disease. (Photo courtesy Steve McCaw)



Daniel Shaughnessy, Ph.D., is a Health Scientist Administrator for the NIEHS Exposure Biology Research Program. (Photo courtesy Steve McCaw)



Like other scientists in NTP, Darlene Dixon, D.V.M., Ph.D., head of the Molecular Pathogenesis Group, is interested in how exposome science intersects with the studies in her lab. (Photo courtesy Steve McCaw)



Scott Masten, Ph.D., director of the NTP Office of Nominations and Selection, is interested in applying exposome research to the prioritization of substances studied by the NTP. (Photo courtesy Steve McCaw)

Research supported by NIEHS informs policy and regulatory discussion

By Eddy Ball

NIEHS-funded researchers found themselves, this winter, at center stage in the national discussion concerning policy and regulatory issues related to environmental public health.

In an [article](#) released Dec. 24, 2013, underscoring the long-term effects of environmental exposure on major public health problems, former New Jersey Governor Christine Todd Whitman (1994-2001) pointed to three large-scale studies, two of them led by NIEHS in-house scientists and grantees. Whitman's editorial, "Assessing the long-term costs of ignoring the environment," appeared in NJ Spotlight, an online news service that features insights and information on issues critical to New Jersey.

A Dec. 16, 2013, New York Times [feature story](#), "F.D.A. questions safety of antibacterial soaps," looked behind the scenes of the new U.S. Food and Drug Administration (FDA) requirement that manufacturers demonstrate the safety of antimicrobial soaps, citing research by scientists supported by the NIEHS Superfund Research Program (SRP).

The story included an interview with SRP grantee [Rolf Halden, Ph.D.](#), director of the Center for Environmental Security at Arizona State University. Along with SRP grantees [Bruce Hammock, Ph.D.](#), and [Isaac Pessah, Ph.D.](#), of the University of California, Davis, and [Robert Tukey, Ph.D.](#), of the University of California, San Diego, Halden is one of several NIEHS-funded scientists who have conducted interdisciplinary studies on the extent of environmental pollution by the antimicrobials triclosan and tricloban, and their potential effects on human health.

Whitman highlights NIEHS research

As the first in the NJ Spotlight collection of year-end essays from those who have sat in the N.J. governor's chair, Whitman's editorial focused on the long-term effects of repeated environmental exposures.

"Recent studies linking various health and economic impacts of environmental contamination should cause policymakers to reevaluate their priorities when it comes to environmental legislation and regulation," Whitman wrote. "Three key areas of research in this area stand out: the connection between certain pesticides and Parkinson's, the correlation between elevated lead in gasoline with crime rates, and the link between air pollution and autism."

Two of the studies that inspired her commentary — one on pesticides and Parkinson's, the other on air pollution and autism — were led by NIEHS-funded researchers. The third study on lead and crime rates cited previous NIEHS-funded research, and acknowledged the editorial assistance of former NIEHS Scientific Director [John McLachlan, Ph.D.](#), of Tulane University.

"In our benevolent mission to grow the economy, we should not be in too great a rush to ignore environmental testing and results," argued Whitman. "The price we pay at the end is much greater than we can afford, both in terms of dollars and human lives."



Whitman also served as administrator of the U.S. Environmental Protection Agency 2001-2003. Like Halden, she takes into consideration both the human health and financial costs of preventable environmental exposures to harmful chemicals. (Photo courtesy of Christine Whitman)

Halden applauds FDA decision

“It’s a big deal that they are taking this on. These antimicrobials have taken on a life all of their own,” said Halden, whose studies have found that triclosan and triclocarban [another antimicrobial] persist even after wastewater treatment. “Their use has really proliferated.”

Studies by Hammock and others have demonstrated that the antimicrobials in liquid and bar soaps can disrupt development in animals, suggesting similar effects in humans. According to [FDA scientists](#), there is no evidence of clearly demonstrated benefits to balance any potential risks from exposure to the chemicals.

The use of these soaps has become widespread, and the antimicrobial chemicals found in them are now also used in a range of consumer products. The [Centers for Disease Control and Prevention](#) found the chemicals in the urine of three-quarters of Americans. Halden said the chemicals accumulate in biota living in surface water and soil, and he pointed to one study that found the chemicals in the breast milk of 97 percent of the women tested.

“These chemicals interfere with the regulation of the human body,” Halden said. “The fascinating thing is that the public has not taken note of this issue.”

Citations:

[Cherednichenko G, Zhang R, Bannister RA, Timofeyev V, Li N, Fritsch EB, Feng W, Barrientos GC, Schebb NH, Hammock BD, Beam KG, Chiamvimonvat N, Pessah IN.](#) 2012. Triclosan impairs excitation-contraction coupling and Ca²⁺ dynamics in striated muscle. *Proc Natl Acad Sci U S A* 109(35):14158-14163.

[Kamel F, Goldman SM, Umbach DM, Chen H, Richardson G, Barber MR, Meng C, Marras C, Korell M, Kasten M, Hoppin JA, Comyns K, Chade A, Blair A, Bhudhikanok GS, Webster Ross G, William Langston J, Sandler DP, Tanner CM.](#) 2013. Dietary fat intake, pesticide use, and Parkinson’s disease. *Parkinsonism Relat Disord*; doi:10.1016/j.parkreldis.2013.09.023 [Online 1 October 2013].

[Mielke HW, Zahran S.](#) 2012. The urban rise and fall of air lead (Pb) and the latent surge and retreat of societal violence. *Environ Int* 43:48-55.

[Roberts AL, Lyall K, Hart JE, Laden F, Just AC, Bobb JF, Koenen KC, Ascherio A, Weisskopf MG.](#) 2013. Perinatal air pollutant exposures and autism spectrum disorder in the children of nurses’ health study II participants. *Environ Health Perspect* 121(8):978-984.

[Schebb NH, Ahn KC, Dong H, Gee SJ, Hammock BD.](#) 2012. Whole blood is the sample matrix of choice for monitoring systemic triclocarban levels. *Chemosphere* 87(7):825-827.

[Venkatesan AK, Pycke BF, Barber LB, Lee KE, Halden RU.](#) 2012. Occurrence of triclosan, triclocarban, and its lesser chlorinated congeners in Minnesota freshwater sediments collected near wastewater treatment plants. *J Hazard Mater* 229-230:29-35.

[Walters E, McClellan K, Halden RU.](#) 2010. Occurrence and loss over three years of 72 pharmaceuticals and personal care products from biosolids-soil mixtures in outdoor mesocosms. *Water Res* 44(20):6011-6020.

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Halden is a professor of environmental engineering. “Public health engineering saves lives and money,” he said. “More than half of humanity’s health problems are dependent, either directly or indirectly, on environmental factors.” (Photo courtesy of Rolf Halden)

International collaboration aims to reduce animal testing

By Catherine Sprankle

Governments around the world require chemical and chemical product testing to identify potential hazards, so that appropriate labeling for safe handling, use, and disposal may be applied. The U.S. shares an interest with other countries to discover more efficient testing methods that reduce or eliminate animal use.

The International Cooperation on Alternative Test Methods (**ICATM**), an international partnership promoting the replacement, reduction, and refinement of alternatives for animal testing, met Nov. 26-27, 2013, at the European Commission Institute for Health and Consumer Protection (IHCP) in Ispra, Italy. NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (**NICEATM**) Director **Warren Casey, Ph.D.**, represented the Interagency Coordinating Committee on the Validation of Alternative Methods (**ICCVAM**) at the meeting. NICEATM provides support for ICCVAM activities, and Casey is an ICCVAM committee member.

“This was an extremely productive meeting,” notes Casey. “The attendees reached some agreements that should facilitate U.S. regulatory agencies’ adoption of methods that have undergone peer review outside the United States, which will result in more efficient testing and less animal use.”

Advancing international adoption of alternative test methods

ICATM facilitates international cooperation in validation, peer review, and development of recommendations on use of new test methods. Casey and the other participants at the meeting made some key decisions to support those goals, including the following agreements.

- Use of the European **TSAR** (Tracking System for Alternative Test Methods Review, Validation, and Approval) as the common tracking database for new test methods developed by ICATM partners.
- The need to define best practices for validation study activities, such as chemical selection, the composition and role of study management teams, and consideration of international classification systems.
- The need to establish and adhere to best practices for compiling data from traditional animal studies for use in validation of new methods, with NICEATM **skin sensitization** and endocrine disruptor databases to serve as trial cases.



The ICATM meeting took place at IHCP, which is located near Lake Maggiore in northern Italy. The IHCP hosts the European Union Reference Laboratory for Alternatives to Animal Testing, which represents Europe in ICATM. (Photo courtesy of the Institute for Health and Consumer Protection)



EURL
ECVAM
European Union Reference Laboratory
for Alternatives to Animal Testing

Linked video:

[Watch a European union video released in January on the science behind development of 21st century safety testing using alternative methods \(11:23\)](#)

(Launches in new window)

Download Media Player:  Flash [↗](#)

In addition to the procedural discussions, the November meeting included updates on current test method evaluation and validation activities in Europe, Japan, Korea, and the U.S.

Casey provided two updates on U.S. activities. One focused on the reinvention of ICCVAM, as outlined by NIEHS and NTP Director Linda Birnbaum, Ph.D. ([see story](#)).

The other summarized recent NICEATM and ICCVAM activities, including evaluations of acute toxicity and eye safety tests; a [workshop](#) focused on reduction and replacement of animal use for *Leptospira* vaccine testing; and activities supporting [Tox21](#) and development of high-throughput screening tests. Attendees at the meeting also had the opportunity to tour the Joint Research Centre's Good Laboratory Practice [facility](#) used to conduct high-throughput screening experiments.

ICATM currently includes member organizations from the European Union, U.S., Japan, Canada, and South Korea. ICATM coordination meetings take place several times a year and provide an opportunity for the five member organizations to discuss activities in their major areas of cooperation. Regular interactions allow the ICATM partners to develop good communications and working relationships, which support collaborations on test method development.

(Catherine Sprankle is a communications specialist with ILS Inc., support contractor for NICEATM.)

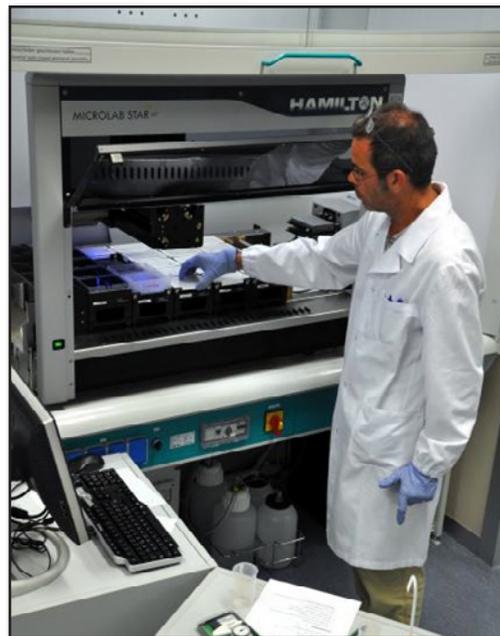
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Harvard SRP collaboration honored for risk communication

By Sara Mishamandani

The [Kids + Chemical Safety website](#), supported in part by the NIEHS-funded Harvard Superfund Research Program (SRP) Research Translation Core (RTC), received the 2013 Risk Communication Award Jan. 15 from the [Alliance for Chemical Safety](#). The site provides up-to-date information on health hazards of chemicals and the safe use of chemicals around children.

“We wanted to find a way to use expertise at the Harvard SRP Center, related to health effects of metals and their mixtures in children, to inform public audiences,” said Katherine von Stackelberg, Sc.D., lead on the Harvard website effort. “We have been partnering with the website for the past year, which was already set up by [Toxicology Excellence for Risk Assessment](#) (TERA). This strategic collaboration allows us to hear directly from parents and others about their concerns.” TERA is an independent, non-profit organization dedicated to scientific collaboration and broad communication of risk science in support of public health protection. It receives funding from a variety of sources, including the chemical industry, government, and the general public.



A researcher operates a staining platform in the high-throughput screening facility at IHCP. Attendees at the ICATM meeting had an opportunity to tour facilities used to conduct high-throughput screening experiments. (Photo courtesy of the Institute for Health and Consumer Protection)

Chemical hazards and children's safety

Through the [Ask an Expert](#) feature on the site, individuals can submit questions or concerns related to chemical exposures and child safety. A group of peer reviewers — from the Harvard SRP (including von Stackelberg), Cincinnati Drug and Poison Information Center, NSF, and TERA — then have the opportunity to weigh in on the response, ensuring peer review of all website content. Articles available on the site include the Ask an Expert responses, as well as topics chosen by reviewers, such as chemical safety concerns that may be receiving media attention.

“I serve as the point of contact for Harvard SRP and send out all requests for review and comment to other SRP researchers,” said von Stackelberg. “People from different organizations, including Harvard SRP, work together constructively to provide information based on the current state of the science.”

Encouraging bidirectional communication

“We were attracted to this partnership because we want to enhance our bidirectional engagement with the general public,” said von Stackelberg. “We disseminate information through the Harvard SRP website, seminars, and social media, but the Kids + Chemical Safety site gives us an opportunity to hear what people want to know about children's environmental health and chemical safety.”

The Harvard RTC is actively exploring cross-disciplinary methods for research synthesis, gathering evidence from many different sources to answer a particular question. The Harvard Center for Risk Analysis, which hosts the Harvard RTC, held a [workshop](#) in October 2013 to discuss methods for research synthesis and the challenges of combining research to promote evidence-based decision-making. At the 2013 Society for Risk Analysis annual meeting, von Stackelberg gave a [presentation](#) on the results of a systematic review using an adverse outcome pathway framework, based on the Harvard research synthesis workshop.

“The opportunity to review and create content for the Kids + Chemical Safety website allows us to put that idea into practice by evaluating scientific evidence and incorporating uncertainty to help parents make their own informed decisions based on scientific findings,” said von Stackelberg.

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

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Harvard SRP RTC co-leader von Stackelberg is working with TERA and other website supporters to answer difficult questions related to children and chemical safety. (Photo courtesy of Katherine von Stackelberg)



The Kids + Chemical Safety site features a variety of topics from the benefits and risks of flame retardants in homes, to chemical risks in children's toys, as well as information to help parents better understand science terminology when researching chemical hazards.

NTP scientists achieve coveted toxicology certification

By Eddy Ball

This winter, two NTP contract scientists and two NTP postdoctoral fellows took an important step along toxicology's professional track, by satisfying requirements for Diplomate of the American Board of Toxicology (DABT) certification. DABT certification often offers an advantage in the job market and career advancement, and has been associated with higher levels of compensation.

The [American Board of Toxicology](#) was established in 1979 to advance standards in the field of toxicology and confer recognition upon those members of the profession who, measured against such standards, demonstrate competence. Certification requirements include a combination of education and experience, as well as a three-part examination.

Several toxicologists at NIEHS and NTP have qualified for the coveted DABT, among them NIEHS and NTP Director Linda Birnbaum, Ph.D., who is the first toxicologist to head the Institute. Birnbaum offered the new diplomates her sincere congratulations.

"This marks a very important milestone in your careers," Birnbaum said. "Achieving the DABT involves a lot of hard work on your part. It also reflects the quality of the science conducted by NTP and the excellent training you've received from our senior scientists here."

The new recipients of the DABT are:

- [Mamta Behl, Ph.D.](#)
- [Arun Pandiri, Ph.D.](#)
- [Michael Boyle, D.V.M.](#)
- [Sheetal Thakur, Ph.D.](#)



Behl is a former NTP fellow and current contract toxicologist in the NTP Systems Toxicology Group, a part of the Toxicology Branch, which oversees rodent studies. (Photo courtesy of Steve McCaw)



An Intramural Research Training Award (IRTA) fellow in the NTP Pathology Group, Boyle is also a Diplomate of the American College of Veterinary Pathologists (DACVP) and a Ph.D. candidate at North Carolina State University. (Photo courtesy of Steve McCaw)



A contract pathologist in the NTP Investigative Pathology Group, Pandiri also holds DACVP certification. (Photo courtesy of Steve McCaw)



Thakur is an IRTA fellow in the NTP Systems Toxicology Group. (Photo courtesy of Steve McCaw)

Diplomates hold initial DABT certification for 5 years, and must demonstrate that they actively practice toxicology, engage in continuing education, and maintain expert knowledge in their field prior to receiving recertification.

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Grantees named AAAS fellows

By Eddy Ball

Four NIEHS grantees will be among new fellows honored this year by the American Association for the Advancement of Science (AAAS). The scientists, who were elected as fellows in the Biological Sciences and Medical Sciences sections, will receive a certificate and rosette Feb. 14 in Chicago, during the AAAS Fellows Forum, which is part of the association's [annual meeting](#).

AAAS is the world's largest general scientific society, and publishes the journal *Science*. Founded in 1848, the society includes more than 261 affiliated societies and academies of science, serving about 10 million people. A nonprofit organization, the society is open to all, and fulfills its mission by advancing science and serving society through initiatives in science policy, international programs, and science education.

The [2013 AAAS fellows](#) include the following distinguished scientists who enjoy support by NIEHS:

- [Frank Gilliland, M.D., Ph.D.](#), is a professor of preventive medicine and directs the Division of Environmental Health within the Keck School of Medicine at the University of Southern California (USC). He is the director of the NIEHS-supported Southern California Environmental Health Sciences Center.
- [Oliver Hankinson, Ph.D.](#), who holds an NIEHS grant for training in molecular toxicology, is a professor of pathology and laboratory medicine at the University of California, Los Angeles. In 2000, he became the founding director of the university's doctoral program in molecular toxicology.
- [Michael Kastan, M.D., Ph.D.](#), is executive director of the Duke Cancer Institute at Duke University. Along with grants from the National Cancer Institute, Kastan receives NIEHS support for studies of cellular stress response signaling pathways.
- [Rob McConnell, M.D.](#), is a professor of preventive medicine and deputy director of the NIEHS/EPA-supported Children's Environmental Health Center at USC. He is the lead researcher on two NIEHS grants.



Gilliland studies asthma etiology and exacerbation, lung function growth in children, respiratory illness-related school absenteeism, and lung cancer etiology and early detection. (Photo courtesy of Steve McCaw)



Hankinson received the Society of Toxicology's 2011 Distinguished Toxicology Scholar Award. His research focuses on how environmental pollutants, such as 2,3,7,8-tetrachlorodibenzo-p-dioxin and benzo[a]pyrene, can cause cancer and other diseases. (Photo courtesy of Oliver Hankinson)



Kastan is also a professor in the departments of pharmacology and cancer biology at Duke University, as well as pediatrics. (Photo courtesy of Michael Kastan)



McConnell's research has demonstrated connections between traffic-related air pollution and such conditions as asthma and autism. (Photo courtesy of Robert McConnell)

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NIEHS fellow begins career in educational writing

By Aleksandra Adomas

After completing postdoctoral training in the NIEHS Laboratory of Neurobiology, Jacqueline de Marchena Powell, Ph.D., began a career as a medical science writer and editor December 2013 with Education and Training Systems International (ETSI). Located in Chapel Hill, N.C., ETSI provides training materials for pharmaceutical, biotech, and medical device companies. Powell's first project was to develop an educational module for sales representatives and physicians on disorders of the reproductive system.

Following in-depth research on career options in life sciences, Powell focused on writing. A series of informational interviews reassured Powell that a writing job would be a good match for her personality, values, and skills, as well as a potential stepping-stone to other positions.

Negotiation power

When Powell first learned about ETSI from her professional contacts, she was not discouraged by the lack of vacancy announcements on the company website and submitted her resume with a general inquiry about employment opportunities. That led to an online writing test, then an invitation to interview.

Seeking strategy advice and support, Powell met with Denise Saunders, Ph.D., career counselor with the NIH [Office of Intramural Training and Education](#). Powell recalls it as a crucial meeting. "I knew I might need to accept a pay cut for an entry-level industry position, so I made a list of other things that were important to me," she said.

Saunders explained that in the hiring process, the only time the job seeker has leverage is immediately after an offer is extended. This knowledge gave Powell confidence to engage in negotiations once she received the job offer, and she was able to successfully negotiate flexible working hours.

NIEHS community support

Powell expressed gratitude for the support she received from the NIEHS community during her job search. “I’m very fortunate to have met a number of outstanding mentors,” she explained. Saunders guided her through job offer negotiations. Tammy Collins, Ph.D., director of the NIEHS [Office of Fellows’ Career Development](#), offered Powell assistance in brainstorming potential career options.

Huei-Chen Lao, a biologist on detail as a science education and outreach coordinator in the NIEHS [Office of Science Education and Diversity](#), showed Powell that marketing skills are vital when looking for a job.

Eddy Ball, Ph.D., former Environmental Factor (e-Factor) editor, not only helped Powell with gaining writing experience, but also gave her constructive advice on expanding her professional network. “During the interview, I used the e-Factor experience to highlight my writing skills and interest in a writing career,” Powell said. “Summarizing research papers for the Intramural Papers of the Month section [of the newsletter] was helpful when I was asked to describe my own research in lay language. It also demonstrated my ability to understand complex concepts and translate them for a nonscience audience,” she added.

Finally, Powell gratefully acknowledged the support she received from Patricia Jensen, Ph.D., head of the [NIEHS Developmental Neurobiology Group](#). During her 3 1/2 years of postdoctoral training, Powell worked with Jensen, studying a set of neurons in the mouse brain that release norepinephrine, an important neuromodulator. Powell was involved in the development of two mouse lines that allow selective manipulation of different subpopulations of norepinephrine-releasing neurons.

(Aleksandra Adomas, Ph.D, is a former research fellow in the NIEHS Laboratory of Molecular Carcinogenesis.)

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Postdoc transitions into career in biopharmaceuticals

By Sheila Yong

Jeremy Weaver, Ph.D., explored many career options during his time as a postdoctoral fellow at NIEHS. He found his perfect match in a position as a process development scientist at Grifols Therapeutics Inc., which he began Jan. 13.



Powell’s advice to other postdoctoral fellows is to start applying for jobs early on in the postdoctoral training, to use LinkedIn to open up contacts and research position titles, and to attend local networking events like the ones organized by the [American Medical Writers Association](#) and the [North Carolina Regulatory Affairs Forum](#). (Photo courtesy of Steve McCaw)

Weaver obtained his Ph.D. in Animal Science from Cornell University, and joined the NIEHS Laboratory of Signal Transduction in November 2010. His research in the [Inositol Signaling Group](#), led by Stephen Shears, Ph.D., focused on enzymes that synthesize inositol pyrophosphates, and how these small signaling molecules regulate cellular processes in response to environmental insults and disease development.

“I was initially interested in careers in academic or government research, because I enjoy both bench science and the opportunity to mentor young scientists,” Weaver said. However, upon further research, he discovered other career possibilities in industry that align better with his personal values, while still allowing him to pursue his passion in scientific research and mentoring.

The right training for the job

Weaver’s new position is a technically challenging one. It involves purifying candidate protein drugs from various expression systems and blood plasma to be used in clinical trials. For that reason, his work is subject to stringent experimental and quality control.

At NIEHS, Weaver acquired extensive knowledge about protein purification platforms and skills that are transferrable to his new job. Besides learning new skills in the lab, Weaver also received assistance from the staff members at the NIEHS protein expression core facility, who shared their expertise with him and helped broaden his research experience.

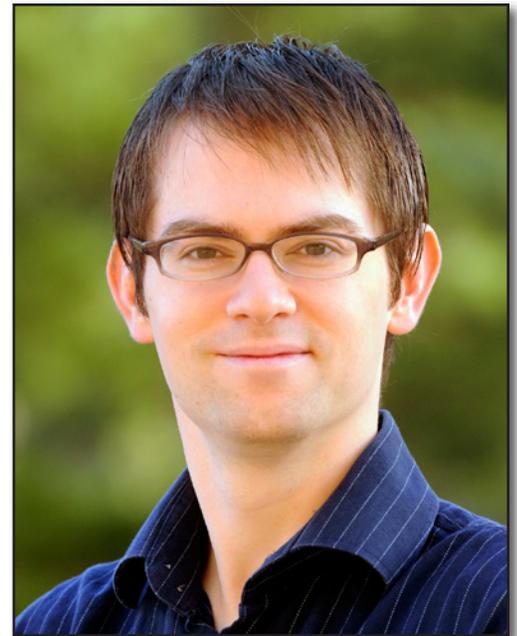
Weaver is also grateful to Shears for allowing him the flexibility to pursue his research and career interests. He said that Shears took an active interest in ensuring his success, and was always available to offer advice. “Steve had my best interests at heart, and was actually the one who encouraged me to consider careers in industry,” he noted.

Shears considers Weaver a valuable member of his team. “Jeremy was not only fearless at learning techniques in our group that were new to him, but also made significant improvements to them on several occasions,” he commented. Shears is confident that Weaver will continue to excel in his future scientific endeavors.

Career development and networking

Apart from his research responsibilities at NIEHS, Weaver also invested effort in building his professional network by attending networking events in the Triangle area, including those at the NC Biotechnology Center and [Triangle Biotech Tuesdays](#). He also frequently participated in events within NIEHS, such as the brown bag lunches and coffee hour organized by the NIEHS Trainees Assembly. These events allowed him to interact with professionals and fellow trainees with similar career aspirations. “I learned how to present myself and my research to other scientists, as well as to reflect on my own strengths and weaknesses,” Weaver explained. These skills helped him tremendously during his job interview.

Weaver found his job the old-fashioned way — by answering an advertisement. Nevertheless, the career development opportunities at NIEHS gave him an edge over other applicants. He credited Tammy Collins, Ph.D., director of the Office of Fellows’ Career Development, for reviewing his resume, as well as various career-related workshops that helped prepare him for the job market.



Weaver hopes to return in April, to host the discussion panel on careers in contract research organizations at the NIEHS Biomedical Career Fair. He looks forward to getting together with his former fellow trainees again and sharing his new work experience. (Photo courtesy of Steve McCaw)

In particular, he cited the management boot camp and the writing workshop by Duke University Professor George Gopen, J.D., Ph.D., as two of the highlights. “While attending these events was a small time investment on my part, it caught the interviewers’ attention,” he said.

As a process development scientist at Grifols, Weaver looks forward to participating in the drug development process. “Grifols organizes Patient Day, an annual event which invites patients using medications from the company to visit the site,” he explained. “Having the drugs I purify go beyond clinical trials and help improve patients’ lives would be an absolutely rewarding experience.”

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

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2014 calendar features artwork by NIEHS postdoc

By Eddy Ball

This year, September will be a special month for [Sheila Yong, Ph.D.](#), a visiting fellow in the NIEHS Inositol Signaling Group. That’s when her artwork, which is part of the 2014 desk calendar distributed by the laboratory supply company Abcam, will be on display in offices, labs, and cubicles around the world.

Yong was one of 13 scientist-artists whose work was chosen in the Abcam Molly Calendar Art Contest held last summer. Contestants were invited to submit original artwork featuring Abcam’s mascot, Molly. The company describes the mascot as a molecular Dolly, referring to the cloned sheep featured on front pages worldwide in 1989, when the firm was founded in Cambridge, U.K.

“The contest was whimsical and lots of fun,” Yong said. “Like the others, my entry, ‘Molly’s Lambs First Day at School,’ satisfied the only specific requirement — that the artwork include Molly, with her molecular space-filled torso and antibody legs. The rest was completely up to the contestants.”

The calendar shows Molly in a variety of settings, including working in her lab, sitting at home by the fireside, soaring in the air, and relaxing on Miami Beach.

Winners included scientists from the U.S., Canada, U.K., Spain, and Japan. The prizes are modest — a \$45 cash voucher, personalized tee shirt, and exclusive Molly print created by the company’s Molly design expert. But, each month, the winning artist will also be featured with a biography on the Abcam calendar [page](#), where the 2014 calendar is available free of charge.

According to Abcam representative Francesca Axe, the calendar can also be requested by email at mailrequests@abcam.com with the subject line “calendar – [country of residence],” for example “calendar – US.”



The cover suggests the calendar’s whimsical tone, with Molly frolicking in extracellular space. (Photo courtesy of Abcam)



Winning the contest was an early holiday present for Yong, who proudly displays her cash voucher, Molly print, and her page from the calendar. “Participating in the contest reminded me of how much I used to enjoy art,” she noted. In addition to her experiments at the bench in signal transduction, she is a veteran contributing writer for the NIEHS Environmental Factor, as well as a translator fluent in Mandarin Chinese. (Photo courtesy of Steve McCaw)

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Biostatistics intern reaches national semifinals for science competition

By Ian Thomas

NIEHS summer intern Mitas Ray was recognized in December 2013 as one of 300 semifinalists for the prestigious Intel Science Talent Search (Intel STS) competition. A senior at Enloe High School in Raleigh, N.C., Ray was selected from a pool of 1,794 entrants, representing 489 high schools in 45 states and the District of Columbia, as well as seven overseas schools.

“As early career milestones go, this was a huge honor,” said Ray, who got the news of his nomination via text while in class. “I have to give a lot of the credit to my mentors at NIEHS. They were always there for guidance and support, but, in the end, they gave me the space I needed to really run with this project and make it my own.”

Intel STS is among the nation's most distinguished precollege science competitions, boasting an impressive list of alumni, many holding some of the world's most coveted scientific awards, including the Nobel Prize and National Medal of Science.

All about the numbers

Ray spent the majority of his summer working in the [NIEHS Biostatistics Branch](#), tasked with exploring statistical issues of relevance to environmental health. There, under the tutelage of [Keith Shockley, Ph.D.](#) and [Grace Kissling, Ph.D.](#), Ray delved heavily into the realms of computer science and chemical testing, while developing his award-winning research.

“A lot of the processes by which we test chemicals today are extremely limited, because of their high cost and low throughput,” said Ray. “The goal of this project was to design a new method using computer science and cell-based assays that would allow us to test a wide range of chemicals at once and in a fraction of the time.”

“Working with Mitas was a wonderful experience,” said Keith Shockley, Ph.D., one of Ray's mentors at NIEHS. “He's a really energetic and self-motivated person, and if his time with us is any indication, he's got a bright future ahead of him in science.”

Looking forward

In addition to his semifinalist nomination, Ray also earned a \$1,000 cash prize for his work — a prize that Intel STS matched, dollar for dollar, and presented to Enloe for its commitment to educational excellence in science, math, and engineering.

“I think the greatest thing about an honor like Intel STS is that it pushes you to work even harder than you already do,” said Ray. “That's an admirable thing in any field, much less one like computer science, where things are always changing.”

Intel STS is a program of the Society for Science and the Public, a nonprofit membership organization dedicated to public engagement in scientific research and education.

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

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Ray hopes to study computer science at the University of California, Berkeley; the Massachusetts Institute of Technology; or Carnegie Mellon University. (Photo courtesy of Steve McCaw)



Ray, left, and Shockley discuss the finer points of Ray's project. (Photo courtesy of Steve McCaw)

Science Notebook

Using nanomedicine to improve human health

By Robin Arnette

Moore's Law states that the number of transistors on a computer chip will double approximately every two years. Since Intel co-founder Gordon Moore offered that assessment in 1965, the development of smaller and smaller transistors has allowed computing power to double every 18 months. By borrowing the manufacturing techniques of the microelectronics industry, today's biomedical and chemical engineers are designing better medicines and vaccines using nanotechnology.

One of the researchers at the forefront of nanomedicine is Joseph DeSimone, Ph.D., founder of [Liquidia Technologies](#), a nanotechnology company based in Research Triangle Park (RTP), N.C. As part of the 2014 NIEHS Distinguished Lecture Series, DeSimone visited the Institute Jan. 24 to talk about making organic particles for therapeutics. Gary Bird, Ph.D., staff scientist in the NIEHS Calcium Regulation Group, hosted the seminar.



DeSimone is the Chancellor's Eminent Professor of Chemistry at UNC, William R. Kenan Jr. Distinguished Professor of Chemical Engineering at NCSU, and founder of several local biotech companies. (Photo courtesy of Steve McCaw)



Linked video:
[Watch DeSimone discuss the process of making therapeutic nanoparticles at his 2011 TEDMED talk. \(19:44\)](#)

(Launches in new window)

Download Media Player:  Flash [ⓧ](#)

Perspective rooted in materials science

DeSimone is a materials scientist by training and holds professorships at the University of North Carolina at Chapel Hill and North Carolina State University. He has spun off several other biotech firms, but the basis for all of his entrepreneurial pursuits is the work his team performed in his university [lab](#).

At the beginning of his talk, he provided context for how scientists have accelerated the growth of nanotechnology. "In the early 70s, you could only fit about 2,300 transistors into the couple of square centimeters of a computer chip, because each transistor was a little bigger than a red blood cell — about 10 microns," DeSimone said.



NIEHS and NTP Director Linda Birnbaum, Ph.D., shared DeSimone's excitement about bringing down the cost of vaccines, during the question-and-answer session. (Photo courtesy of Steve McCaw)

“Today’s chip has billions of transistors in that same area, so, biologically, Moore’s Law has gone from the size of a single cell to a virus particle.”

Using nature as a template

DeSimone said that the inspiration for the size, shape, chemical properties, and mechanics of his nanoparticles comes from nature. For instance, after studying how a helicopter maple seed creates aerodynamic lift, he shaped one group of particles like it. By mimicking a maple seed’s natural autorotation when falling through air, these particles float effortlessly through the lung’s airway when inhaled, delivering their pharmaceutical content.

In another example, DeSimone and his team examined the physical properties of red blood cells. He explained that these cells are soft when young, permitting them to squeeze through extremely small sinusoids in the spleen. As these cells near 120 days, the average life expectancy of a red blood cell, they stiffen, becoming unable to travel through the spleen.

“That’s how the body removes old red blood cells, so using some of characteristics of mechanobiology allows us to understand how to evade biological barriers,” DeSimone said. Mechanobiology is an emerging field of science at the interface of biology and engineering.

PRINTing better medicines and vaccines

After the particle design phase is done, the next step is to produce large quantities of particles using a technique DeSimone’s team developed. The process, known as particle replication in non-wetting templates, or PRINT, physically etches a form into silica, pours liquid fluoropolymers into it, and zaps the liquid with light so that it hardens.

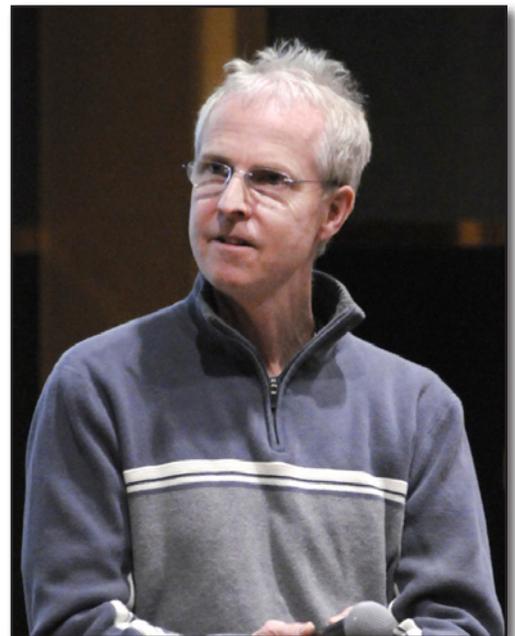
At this point, DeSimone said it essentially looks like an ice cube tray, but on the nano scale. Then, technicians fill the tray with a liquid form of a cancer drug, antibiotic, or whatever therapeutic agent they want to study. Other processing steps ultimately lead to the creation of particles having the precision and uniformity of microcircuits.

“We converted this to a GMP [good manufacturing practice]-compliant process,” DeSimone said, referring to the manufacturing process at the Liquidia facility housed in RTP. “It allows us to deliver a drug strategy of chemotherapeutics, vaccines, and immunostimulatory approaches for cancer.”

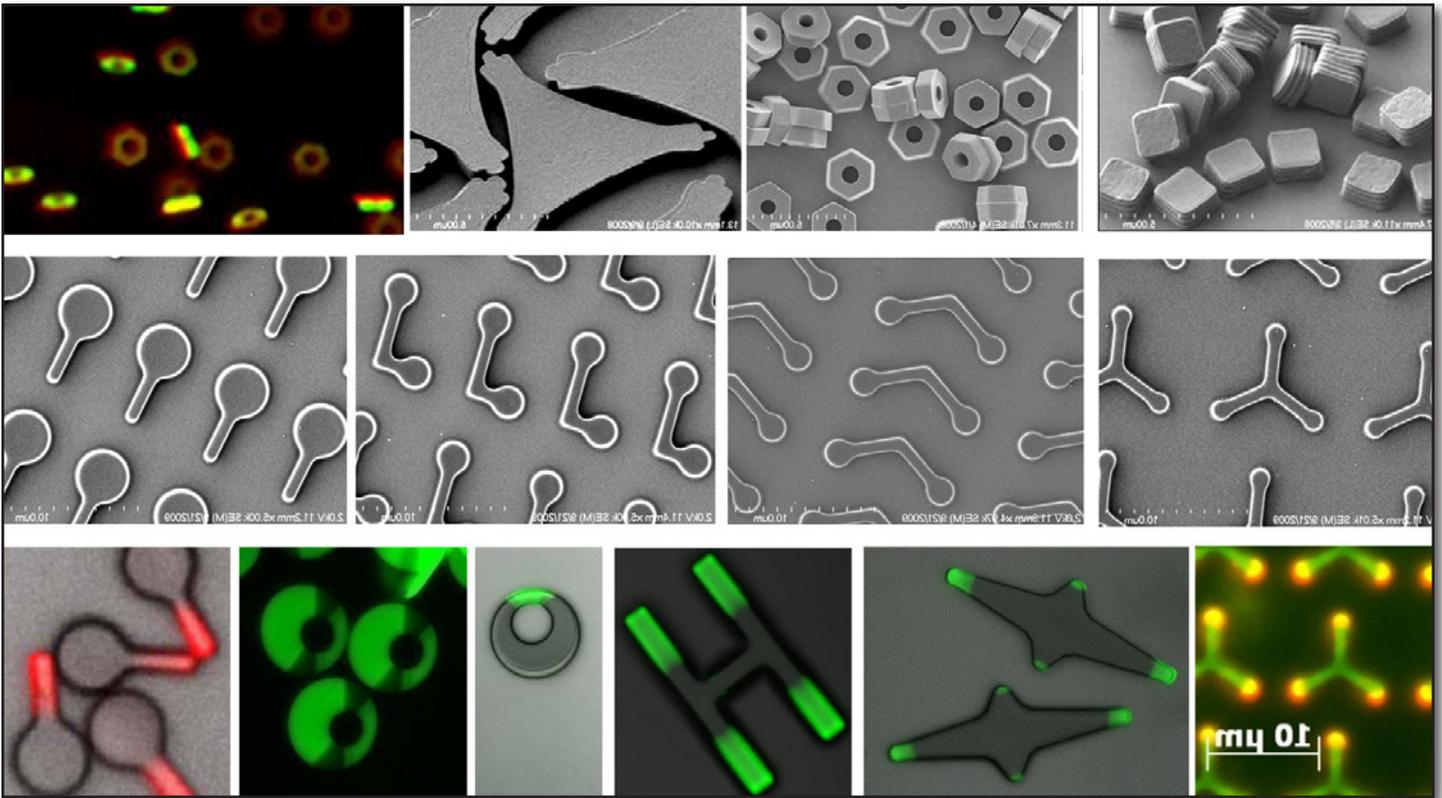
The PRINT method has been so successful that Liquidia received the first ever equity investment in a for-profit biotech firm from the Bill and Melinda Gates Foundation. When DeSimone and Bill Gates met 3 1/2 years ago, both men came away from the meeting believing they could use this technology to drive down the cost of vaccines and improve global access.



NIEHS Scientific Director Darryl Zeldin, M.D., a lung disease specialist, was especially interested in DeSimone’s inhalation data. (Photo courtesy of Steve McCaw)



Bird said DeSimone’s research has had an enormous impact on bridging engineering and nanomedicine. (Photo courtesy of Steve McCaw)



DeSimone's team can produce nanoparticles with a variety of sizes and shapes using PRINT technology. (Graphic courtesy of Joseph DeSimone)

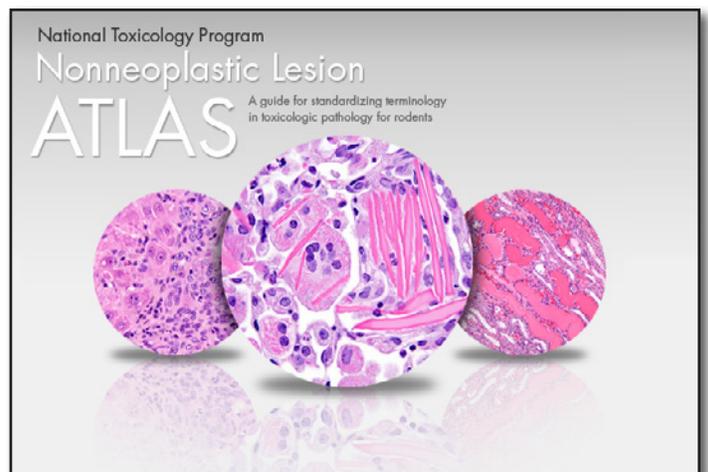
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New NTP atlas helps standardize nonneoplastic lesion diagnoses

By Robin Mackar

In January, NTP debuted a new web-based resource that will help pathologists worldwide better diagnose, record, and discuss nonneoplastic rodent lesions. Nonneoplastic lesions, or noncancer lesions, can be precursors to cancer and can also be associated with life-threatening, noncancerous diseases, such as pulmonary fibrosis, and are therefore important findings in toxicity and carcinogenicity studies.

This new tool, the NTP [Nonneoplastic Lesion Atlas](#), is available online and is highlighted in a new [commentary](#) by NTP staff in the peer-reviewed journal *Toxicologic Pathology*.



When completed, the Atlas will consist of thousands of high-quality, zoomable images and diagnostic guidelines arranged in 56 sections organized by organ system, each covering a particular organ or tissue. The subsections on bone marrow in the hematopoietic system; liver and gallbladder in the hepatobiliary system; skin in the integumentary system; brain, nerve, and spinal cord in the nervous system; and the ureter and urinary bladder in the urinary system section are already available.

In addition to the digital images, each lesion page includes the NTP recommended terminology, histopathologic descriptions, and other useful information about the lesions, diagnostic guideline recommendations, and references.

An authoritative resource

“Having a resource that toxicologists and pathologists all over the world can use to speak the same language when diagnosing nonneoplastic lesions in rats and mice will be invaluable to the NTP and to the field,” said [Robert Sills, D.V.M., Ph.D.](#), head of the NTP Cellular and Molecular Pathology Branch.

Sills conceived the atlas and, along with his team, helped bring the project to fruition. “Being able to actually zoom in and see, in exquisite detail, what these lesions look like and knowing the preferred NTP diagnostic term for each lesion will lead to more standardization of study results,” he explained.

The images have been compiled mostly from the NTP archives, a state-of-the-art facility that the NTP has been supporting since 1984 to house its expansive collection of research specimens and supporting data from NTP studies.

“The pathology community looks to NTP to develop these kinds of resources,” Sills said. The atlas helps improve the organization and diagnostic consistency of the NTP database and can also be used by other laboratories to standardize their diagnostic strategy and improve their own databases.

Establishing the gold standard

“The NTP has long been known for establishing the diagnostic criteria and terminology for neoplastic lesions in rodent cancer bioassays and we wanted to establish the same standards for nonneoplastic lesions,” said NTP pathologist [Mark Cesta, D.V.M., Ph.D.](#), an editor and author of the Toxicologic Pathology paper and the atlas. Cesta adds that nonneoplastic diseases are also a major cause of morbidity and mortality in humans, with some of these diseases thought to be brought on by environmental causes, making this resource valuable to medical researchers worldwide, as well as to NTP study pathologists.

“We know that many lesions seen in human diseases have relevant counterparts in NTP rodent toxicity and cancer studies,” Cesta said. “This will be a living document that we will keep updating as new information about diagnosing nonneoplastic lesions becomes available,” Sills said. “It will become the must-have resource for every pathologist and a great training tool for the next generation of toxicologic pathologists.”

Collaborative effort

“This was truly a group effort,” said NTP Associate Director John Bucher, Ph.D. “We couldn’t have accomplished this without drawing upon the expertise of many.” Each section of the Atlas was extensively reviewed by NTP pathologists and by independent pathology experts who specialize in specific organ systems.



The NTP Nonneoplastic Lesion Atlas was the brainchild of Sills. It will be used by NTP and its many pathology partners to standardize lesion diagnosis, terminology, and the way lesions are documented. It is expected to improve understanding, consistency, and accuracy between pathologists and laboratories. (Photo courtesy Steve McCaw)

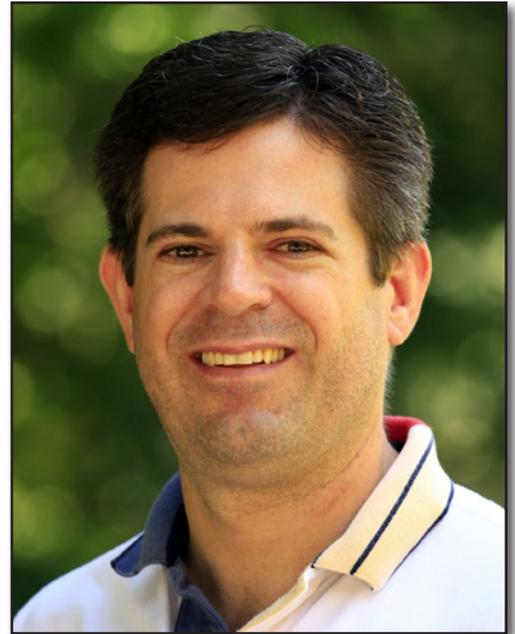
Additionally, experts in web-based technologies were also called upon to create the online searchable database. The Atlas also went through several focus groups before launching to ensure usability. “I think the Atlas will be a tremendous resource to the NTP and many others,” Bucher added.

NTP is proactively creating awareness about the Atlas among key stakeholders. The NTP will host an exhibitor session at the Society of Toxicology [annual meeting](#) in March, offer demonstrations during a NTP satellite symposium at the Society of Toxicologic Pathology [annual symposium](#) in June, and provide several demonstrations and webinars for NIEHS and NTP staff, grantees, international users, and pathology students, among others.

Citation: Cesta MF, Malarkey DE, Herbert R, Brix A, Hamlin M, Singletary E, Sills RC, Bucher JR, Birnbaum LS. 2014. The National Toxicology Program web-based Nonneoplastic Lesion Atlas: A global toxicology and pathology resource. *Tox Path* 42:458-460.

(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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Cesta has been instrumental in reviewing and coordinating all the content for the new atlas, and has worked with a dedicated team of federal and contract staff to bring the atlas to fruition. When completed, the atlas will contain 56 sections and thousands of images. (Photo courtesy Steve McCaw)

Scientists begin to fill in the gaps in understanding about fracking

By Eddy Ball

NIEHS-funded scientists are looking more closely at the impact of hydraulic fracturing on air and water quality in drilling-dense areas of Ohio and Colorado.

Offering the prospect of energy independence and new sources of income for landowners, hydraulic fracturing, or fracking, has spread many times faster than has research into the potential health effects of the chemicals used in the practice. Along with an upcoming seminar at the University of Pennsylvania ([see text box](#)), these new studies are helping raise awareness of the potential environmental public health impact of this unconventional natural gas drilling method.

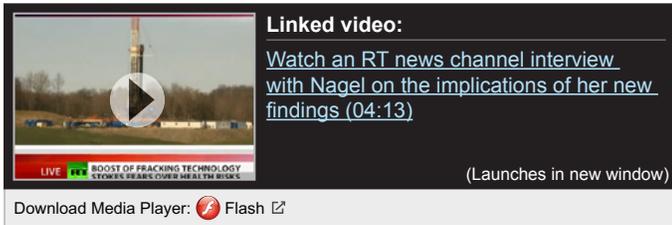
New studies build on ongoing research

In a [study](#) published Dec. 16, 2013 in the journal *Endocrinology*, a team of scientists led by University of Missouri Associate Professor [Susan Nagel, Ph.D.](#), identified, for the first time, dozens of chemicals used in hydraulic fracturing for natural gas that may have adverse effects on human health, by disrupting estrogen and androgen action.



Nagel, a reproductive biologist specializing in estrogenic actions, reported finding moderate levels of endocrine-disrupting chemicals in samples from the Colorado River, the basin where the Garfield County fracking sites drain. The county has more than 10,000 active wells. (Photo courtesy of the University of Missouri)

With a new grant from NIEHS, a team of researchers from the University of Cincinnati and Oregon State University is laying the foundation for a community-based participatory research pilot study of air quality and fracking in Carroll County, Ohio ([see story](#)).



Linked video:
[Watch an RT news channel interview with Nagel on the implications of her new findings \(04:13\)](#)

(Launches in new window)

Download Media Player:  Flash [↗](#)

Trying to answer nagging questions about safety

“With fracking on the rise, populations may face greater health risks from increased endocrine-disrupting chemical exposure,” Nagel was quoted as saying in a Los Angeles Times [article](#). “I’m not an alarmist about this, but it is something the country should take seriously.”

The researchers compared 39 water samples, from known incident sites, that had experienced some sort of spill or accident related to fracking in a drilling-dense region of Garfield County, Colo., with samples from drilling-sparse areas in Missouri and Colorado without spills. They found that drilling-dense region water samples showed as much as two times greater estrogenic, anti-estrogenic, or anti-androgenic activity than water from reference sites, where activity was dramatically lower.

Nagel received NIEHS [funding](#) in 2011 to study the DNA methylation pattern in the endometrium of women with endometriosis. With a previous grant, she examined the effects of prenatal endocrine-disrupting chemical exposure and altered expression of endometriosis related genes in a mouse model. She said her ultimate goal is to link these two studies, by identifying markers of exposure in mice and connect them with markers in women.

As Nagel and her colleagues readily admit, the kind of early-stage research her group conducted in Colorado cannot produce conclusive results, and more studies are needed to fully understand the implications of their findings. In an interview with RT News following publication of the study, she said, “There is a real dearth of information on the health impacts of this entire process.”

The team showed strong associations between fracking sites and the presence of chemicals with endocrine-disrupting effects in water, but not a clear-cut, cause-and-effect link, as critics were quick to point out in a statement from [Energy in Depth](#), one of several defensive responses from industry groups.

Others, such as editors of the Raleigh (N.C.) News and Observer, in a Dec. 19, 2013 [editorial](#), have cited Nagel’s findings as one more reason to proceed with caution, in regard to regulations for proposed fracking operations in their state. “The state’s Mining and Energy Commission should err on the side of disclosure and caution, as it writes the rules for North Carolina,” they concluded.

Upcoming symposium on hydraulic fracturing

The University of Pennsylvania Center of Excellence in Environmental Toxicology (CEET) and the Center for Public Health Initiatives are co-hosting a [symposium](#) Feb. 18 at the Smilow Center for Translational Research, exploring the impact of unconventional natural gas drilling operations on the environment and public health.

CEET is an environmental health sciences core center funded by NIEHS. The symposium is intended to engage many different stakeholders concerning hydraulic fracturing, and educate participants on the process and effects on the environment and public health. The meeting will also profile ongoing research on this topic, and end with a panel discussion on citizens’ concerns. In addition to presentations by NIEHS grantees during the symposium, the program will conclude with remarks on future directions by NIEHS Senior Medical Advisor Aubrey Miller, M.D.

[Registration](#) is free but required.

Citation: Kassotis CD, Tillitt DE, Wade Davis J, Hormann AM, Nagel SC. 2013. Estrogen and Androgen Receptor Activities of Hydraulic Fracturing Chemicals and Surface and Ground Water in a Drilling-Dense Region. *Endocrinology*; doi.org/10.1210/en.2013-1697 [Online 16 December 2013].

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Community engagement drives new pilot study on fracking and air quality

By Eddy Ball

A team of NIEHS-funded researchers met with citizens of Carroll County, Ohio, Jan. 9 marking one of the first steps in the new one-year, community-engaged pilot study of fracking and air quality.



Linked audio:
[Listen as Carroll Concerned Citizens Chair Paul Freezel describes his group's support for the new study \(0:25\)](#)

(Launches in new window)

Download Media Player: [Quicktime](#)

Hosted by [Carroll Concerned Citizens](#), the team is mounting a recruitment effort for a new NIEHS-funded pilot study of landowners potentially affected by hydraulic fracturing (fracking) in the rural Appalachian Ohio county. The researchers plan to place passive air sampling devices at 4-6 sites on or adjacent to land where gas is being extracted by the unconventional natural gas drilling (UNGD) method ([see fact sheet](#)).

The researchers from the University of Cincinnati (UC) and Oregon State University (OSU), led by UC Professor [Erin Haynes, Dr.P.H.](#), are also recruiting individuals to wear wristband personal monitors that can measure their exposure to some 1,000 chemicals in the air, in what has rapidly become the most shale-drilled area in the state.

The study is funded by a grant from NIEHS to the UC Center for Environmental Genetics led by [Shuk-Mei Ho, Ph.D.](#) OSU researchers [Kim Anderson, Ph.D.](#), and [Laurel Kincl, Ph.D.](#), are also funded by NIEHS grants.

The community as a research partner

Haynes explained that the study will address the community's concerns about the potential consequences of fracking at the quickly growing number of sites in the county. "As Ohio's shale gas boom continues, thousands of new pads will be installed, many of which will be in close proximity to homes and businesses," she told reporter Bob Downing for a [story](#) in the Akron Beacon Journal. "Understanding if significant air quality changes occur during the various shale gas operations is important to understanding health risks for humans and livestock."



Haynes is also the director of the NIEHS-funded UC Center for Environmental Genetics Community Outreach and Engagement Core, and director of the Clinical and Translational Research training program. (Photo courtesy of the University of Cincinnati)

In planning the study, Haynes and her team have worked closely with residents of Carroll County. Summary data will be shared following the study's completion. Participants will be informed about their individual monitoring results, which will be kept confidential.

“By emphasizing community participation, we’ll be bringing cutting-edge science directly to the public, bridging the gap between scientists and their communities,” Haynes said. “It is critical that research related to UNGD [fracking] involve key community stakeholders at the outset, as it is their air and water that we’re studying.”

Looking ahead

According to Haynes, the pilot study should be completed by summer, and she is already working toward funding for a larger follow-up study.

“We want to address the question very rigorously and with an open mind,” she said. “We’re not coming with a conclusion in hand — we actually want to see what the data will reveal.” The study will also evaluate the performance of the samplers deployed.

“Additional UNGD research is needed, including water quality, impact on rural roadways and community infrastructure, and UNGD-generated waste transportation and injection into wells,” Haynes explained.

Haynes said she hopes to share the data with the Ohio Department of Natural Resources, which regulates oil and gas drilling in the state, as well as the energy industry. “If we do find something, we hope that they [the industry] would make a change.”

(This story is based in part on an article by Keith Herrell, a public information officer with [healthNEWS](#), the UC Academic Health Center Public Relations and Communications publication.)

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The passive air sampling devices, developed by Anderson’s team for monitoring air quality following the Deepwater Horizon oil spill in the Gulf, can be attached to trees, fence and utility posts, or structures, posing no danger to humans, livestock, or crops. The sampling box is in the shape of a T, weighs 3 pounds, and is 29 inches long by 12 inches wide at the T. (Photo courtesy of Kim Anderson)



The small, lightweight personal samplers are made of silicone, which absorbs chemicals in the air. Researchers can then extract and identify these chemicals. As the cartoons show, participants will wear their bracelets 24 hours a day. (Photo courtesy of Kim Anderson)

Wastewater treatment offers a view into environmental chemicals' risks

By Carol Kelly

Wastewater treatment facilities offer tremendous value as observatories for what chemicals are being produced, consumed, and circulated in our environment, according to new [research](#) from NIEHS grantees Arjun Venkatesan, Ph.D., and Rolf Halden, Ph.D., from Arizona State University (ASU).

“Our study highlights the use of sewage treatment plants as a resource, instead of treating them as a mere decontamination factory,” said Venkatesan, a doctoral research associate in Halden’s [lab](#) at ASU.

Wastewater treatment facilities are the cornerstone effort to keep the nation’s waters clean. Processed solid waste material is a residual of wastewater treatment, and the byproducts labeled biosolids are characterized as treated, tested, and determined safe for land application. These biosolids contain nutrients useful as fertilizers, as well as heavy metals, toxicants, and pathogens.

Testing biosolids

The researchers analyzed biosolids from municipal wastewater treatment plants to identify contaminants of emerging concern (CECs), which are chemicals known to be harmful, but with unknown risk from their presence, frequency of occurrence, or source. Of particular interest to the researchers were chemicals that stay intact during their journey through several phases of wastewater treatment to the biosolids stage. It was important to identify these chemicals, because they are likely to also persist in the environment. Using a nationally representative sample of biosolids collected by the U.S. Environmental Protection Agency (EPA), the researchers detected 123 CECs. The quantities of those chemicals found in the samples can be used to estimate the amount of each originally produced.

“Our study sends a powerful message that the chlorinated, brominated, and fluorinated chemical compounds mass produced today do not biodegrade safely or naturally,” said Halden. “We provide a way to identify toxic priority compounds used daily in large quantities that are prone to accumulation in organisms and people.”



Rolf Halden, Ph.D., is director of the Biodesign Institute Center for Environmental Security; professor in the School of Sustainable Engineering and the Built Environment; and senior sustainability scientist at the Global Institute of Sustainability at ASU. (Photo courtesy of Arizona State University)



Arjun Venkatesan, Ph.D., is currently working on monitoring the occurrence and persistence of emerging contaminants in biosolids, soils, and sediments at ASU. (Photo courtesy of Arizona State University)

Monitoring contaminants

Common chemical screening methods typically do not consider two important risks to people and ecosystems — current chemical production rates and how chemicals behave in real-world biological systems. The researchers believe that their approach, using biosolids to identify amounts and types of chemicals present in the environment, addresses these shortcomings, and should be a welcome addition to the toolbox for risk assessors tasked with prioritizing and managing CECs.

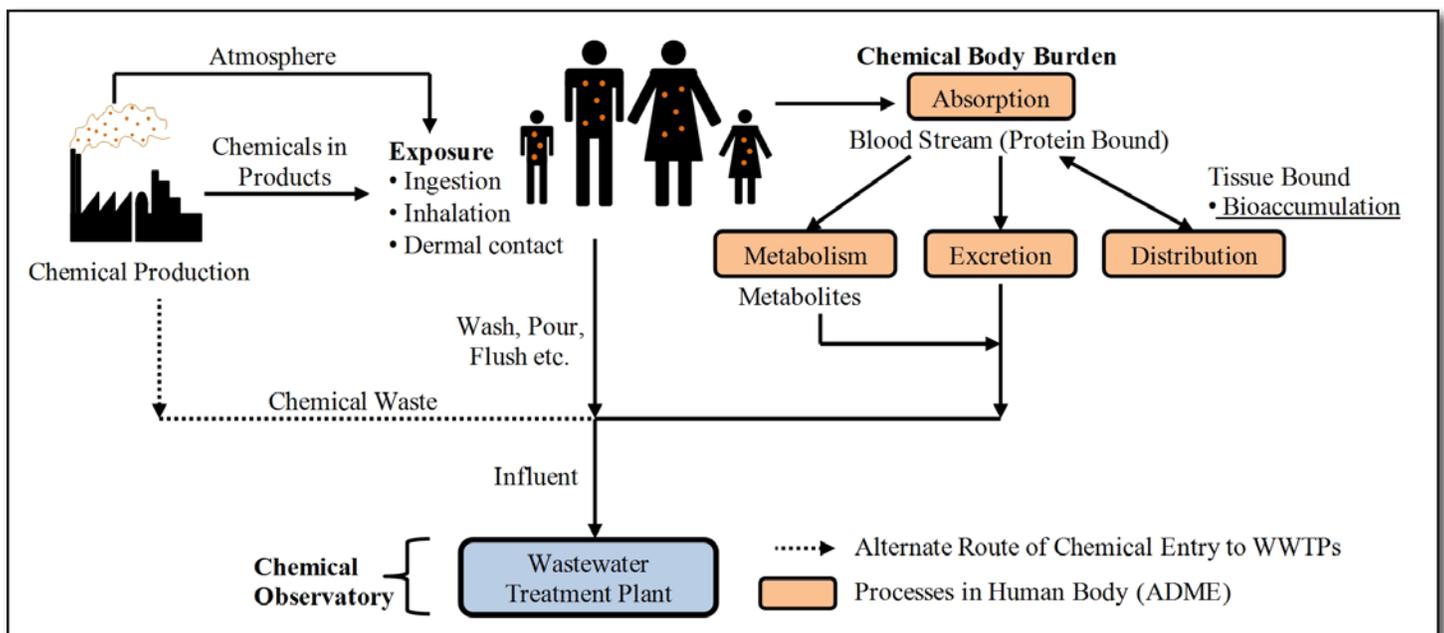
“One could better understand, or even predict, the fate and distribution of mass-produced chemicals in environmental systems, by studying the amount and behavior of those chemicals in sewage treatment plants,” said Venkatesan.

“In addition to monitoring compounds as produced, biosolids can provide estimates of the identity and volume of chemical transformation products resulting from their degradation,” said Halden. “This chemical progeny may be equally, or more, harmful than their parent compounds. One example is nonylphenol, an endocrine disruptor, which is released from the breakdown of alkylphenol ethoxylate detergents.”

Assessing biosolids risk

In the U.S., more than 50 percent of biosolids produced by wastewater treatment are applied to land as an agricultural amendment, according to the EPA. To reduce the amount that must be landfilled or incinerated, they are increasingly used as soil conditioners or fertilizers, or for land reclamation. Various land applications of biosolids take place in all 50 states.

In 2002, the National Research Council said that EPA should conduct studies of the potential health risks, or lack thereof, to workers and residential populations exposed to biosolids from land applications, but this recommendation has not been addressed to date. EPA regulations require periodic monitoring of certain heavy metals and indicator bacteria in solid waste from wastewater treatment, but there is no routine monitoring of other toxicants. The finding of CECs in the study’s biosolids samples underscores the need for improved assessments, according to the researchers.



The researchers’ diagram shows how chemicals move from production, then into and through people, to the wastewater treatment environment. (Courtesy of Arizona State University)

“We need to take steps now to avoid human and ecological health hazards, as well as the costly, long-term contamination of soil and water resources nationwide,” said Halden. “The return on investment can be huge. It’s much more expensive to clean up or treat large-scale environmental contamination than to treat comparatively smaller process streams at the source.”

Citation: [Venkatesan AK, Halden RU](#). 2014. Wastewater treatment plants as chemical observatories to forecast ecological and human health risks of manmade chemicals. *Sci Rep* 4:3731.

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

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High-throughput screening examines multiple effects of 1060 compounds on zebrafish

By *Nancy Lamontagne*

Researchers led by Oregon State University Superfund Research Program grantee Robert Tanguay, Ph.D., used high-throughput screening to analyze 1,060 unique compounds for 22 possible effects on zebrafish embryos.

Researchers said this is one of the largest systematic *in vivo* toxicological studies to date. Using zebrafish to test a large number of chemicals with known structures, and look at a large number of effects, will allow the identification of groups of chemicals that may share the same mechanism of toxicity. Chemicals that show a response in zebrafish can also be further studied using other systems, such as cell-based testing.

“Our study demonstrates that it is now possible to rapidly evaluate the bioactivity of a large number of chemicals in the whole animal,” [Tanguay](#) said.

“The ability to screen more of the chemical space will help the field move closer to relevant whole animal chemical structure-response relationships for predictive toxicology.”

The highly automated and streamlined screening approach developed by the researchers is detailed in a [paper](#) published in the January issue of *Toxicological Sciences*.

A comprehensive screening approach

Using their new approach, the researchers conducted developmental and neurotoxicity screening of 1,060 unique ToxCast phase 1 and phase 2 chemicals. The U.S. Environmental Protection Agency (EPA) National Center for Computational Toxicology [ToxCast program](#) is assessing a large number of chemicals,



Tanguay said that the goal in screening chemicals with zebrafish is not simply to identify hazardous compounds, but to also generate data that will allow prediction of toxicity. (Photo courtesy of Robert Tanguay)

using a diverse set of *in vitro* tests, with the goal of developing cost-effective ways to prioritize the thousands of chemicals for which there is no toxicity information. ToxCast phase 1 chemicals are well-studied chemicals, such as pesticides. Phase 2 chemicals come from a broad range of sources, including industrial and consumer products, food additives, green products, cosmetics, and pharmaceutical drugs.

Using automation to streamline the screening process, investigators employed an automated embryo placement system to load 6-hour-old zebrafish embryos into 96-well plates. Then the researchers added one chemical per well, at six concentrations, with 32 embryos used for each concentration. They monitored various developmental, behavioral, and morphological endpoints, at time points up to 120 hours after fertilization.

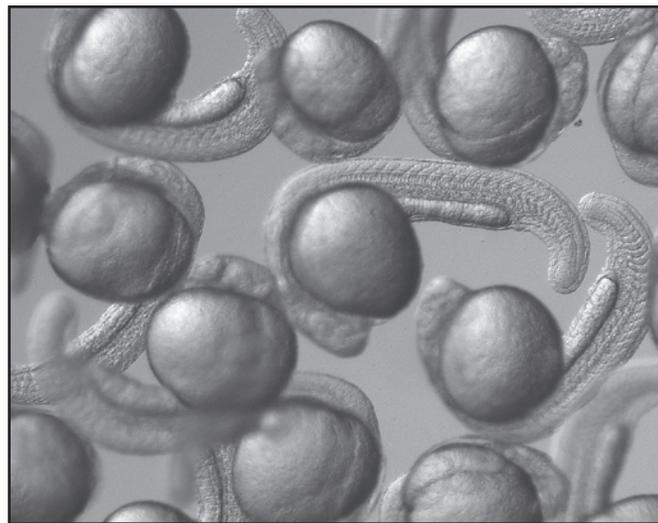
The diversity of the measured endpoints, and the large number of animals per test, increased the screening's sensitivity to detect hazardous chemicals. Also, by measuring 18 of the 22 endpoints simultaneously over time, the researchers could determine relationships between the endpoints and embryonic development. [David Reif, Ph.D.](#), a study collaborator from North Carolina State University, was instrumental in developing novel analysis and visualization tools, such as a custom photomotor response assessment tool to quantify an embryo's response to pulses of light.

Biological responses

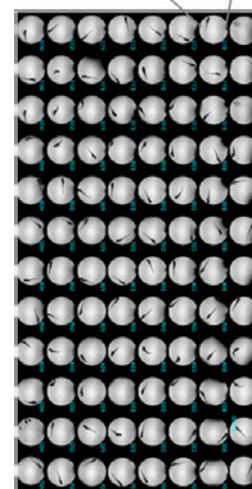
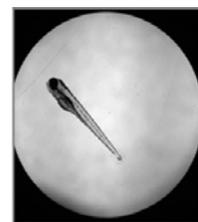
Of the 1,060 unique chemicals evaluated, 487 showed significant biological responses. The data demonstrated that mortality alone was not a good determinant of toxicity, because of the high number of false negatives. Global patterns of variation across the tested chemicals revealed high correlation among endpoints. However, some chemicals, such as the pesticides thiram, ziram, and sodium dimethyldithiocarbamate, affected only a single developmental endpoint in the zebrafish. The researchers concluded that their approach detected adverse responses that other methods would miss.

The scientists continue to refine their experimental approach and to expand the number of chemicals tested. They are working with the EPA, the National Toxicology Program, and others to compare their zebrafish findings with data collected from mammalian cells and whole animal models. The results will allow them to determine the chemical classes for which the zebrafish model is predictive, and to identify the limitations of the model.

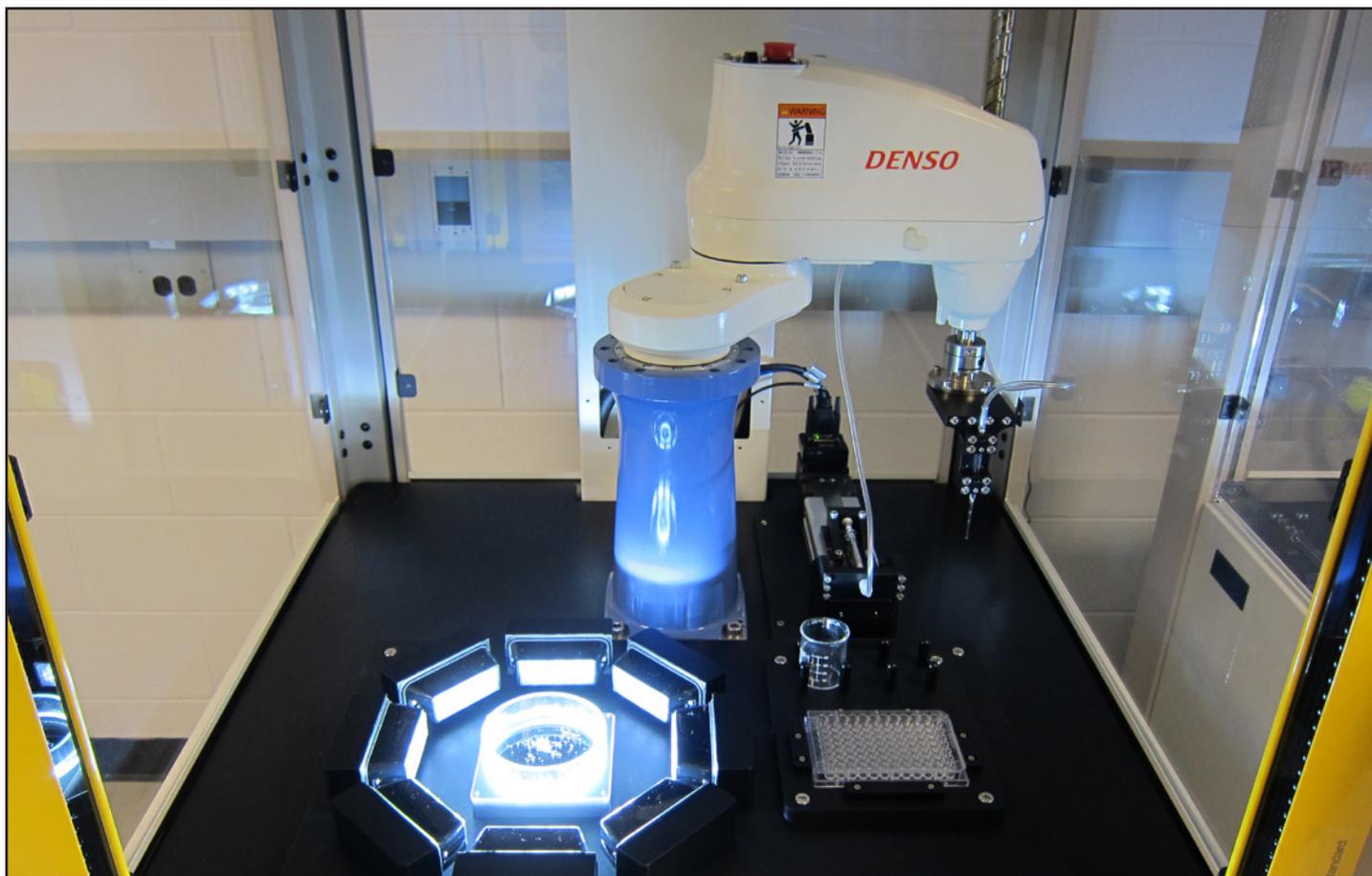
Citation: [Truong L, Reif DM, St Mary L, Geier MC, Truong HD, Tanguay RL.](#) 2014. Multidimensional *in vivo* hazard assessment using zebrafish. *Toxicol Sci* 137(1):212-233.



Zebrafish have several advantages as a model system for toxicology screening. They develop rapidly, have a short life cycle, and are clear for the first few days of life. Also, approximately 84 percent of human genes involved in disease are present in zebrafish. The zebrafish embryos above are 24 hours old. (Photo courtesy of Robert Tanguay)



Each well, above, contains a zebrafish embryo. "This was an enormous study that required a multidisciplinary team composed of mechanical engineers, software engineers, toxicologists, statisticians, and informatics specialists to complete," Tanguay said. (Photo courtesy of Robert Tanguay)



Automation helped improve accuracy and streamline the high-throughput zebrafish screening. The researchers used this robot to load the embryos into 96-well plates. (Photo courtesy of Robert Tanguay)

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

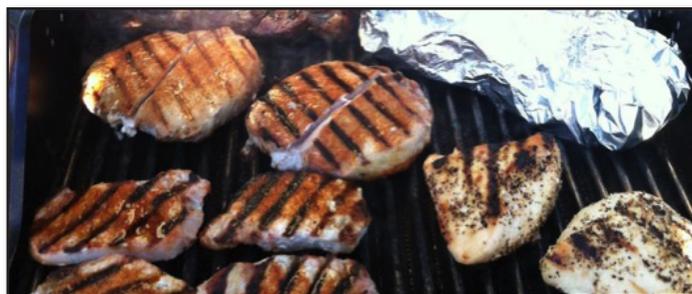
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Study identifies novel compounds more mutagenic than parent PAHs

By Sara Mishamandani

Researchers at Oregon State University (OSU) have discovered novel breakdown products that form when specific high molecular weight polycyclic aromatic hydrocarbons (PAHs) chemically interact with nitrogen. These nitrated-PAHs (NPAHs), which were not previously known to exist, are more mutagenic than their parent PAH compounds.

Mutagens are physical or chemical agents that change the genetic material of an organism, increasing the frequency of mutations. Because many mutations cause cancer, mutagens are likely to also be carcinogens, or agents directly involved in causing cancer.



NPAHs are produced by certain types of chemical reactions, such as those found in grilling meat. (Photo courtesy of Oregon State University)

“Some of the compounds that we’ve discovered are far more mutagenic than we previously understood and may exist in the environment as a result of heavy air pollution from vehicles or some types of food preparation,” said [Staci Simonich, Ph.D.](#), professor of chemistry and toxicology in the OSU College of Agricultural Sciences and Superfund Research Program (SRP) researcher.

The [study](#), led by Simonich, was published in January in the journal *Environmental Science and Technology*.

Understanding the formation of NPAHs

PAHs are present in fossil fuels and are also formed by incomplete combustion of carbon-containing fuels, such as wood, coal, diesel, and tobacco. Many PAHs, such as benzo[a]pyrene, are known carcinogens.

Researchers investigated the reactions of five mutagenic, high molecular weight PAHs in experiments that mimicked conditions similar to those found in the Earth’s atmosphere. They also conducted a theoretical study to understand the formation of NPAHs. The team discovered that nitrogen dioxide (NO₂) and nitrate (NO₃)/dinitrogen pentoxide (N₂O₅) were effective oxidizing agents in transforming PAHs to NPAHs.

According to the [OSU press release](#), NPAHs raise further concerns about the health impacts of heavily-polluted urban air and dietary exposure, although it has not yet been determined in what level the compounds might be present, and no health standards now exist for the compounds.

Rising concerns on health effects

By performing mutagenicity assays, researchers found that, for all the PAHs tested, the NO₃/N₂O₅ exposure resulted in a 6-fold to 432-fold increase in direct-acting mutagenicity.

The study measured the breakdown of specific PAHs by substituting deuterium for hydrogen in the PAHs, causing NPAHs to be formed. Researchers found that the substitution of deuterium lowered the mutagenicity of the NPAHs, suggesting the results from the mutagenicity assays may actually understate the increase in toxicity.

This study grew from PAH pollution work of OSU SRP. As SRP works to identify remediation technologies that break down PAHs in soil and sediment, Simonich is assessing the PAH breakdown products, to determine which remediation techniques minimize the formation of these potentially hazardous products.

The study was supported by NIEHS and the National Science Foundation. Collaborators on the study included researchers from OSU; the University of California, Riverside; and Texas A&M University.

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

Citation: [Jariyasopit N](#), [McIntosh M](#), [Zimmermann K](#), [Arey J](#), [Atkinson R](#), [Cheong PH](#), [Carter RG](#), [Yu TW](#), [Dashwood RH](#), [Massey Simonich SL](#). 2014. Novel nitro-PAH formation from heterogeneous reactions of PAHs with NO₂, NO₃/N₂O₅, and OH radicals: prediction, laboratory studies, and mutagenicity. *Environ Sci Technol* 48(1):412-419.



Simonich has also done extensive work on urban air quality, specifically related to PAHs found in particulate matter, which is a concern for air pollution. (Photo courtesy of Narumol Jariyasopit)

Using teeth to uncover developmental susceptibility to chemical mixtures

By Sara Mishamandani

Manish Arora, Ph.D., from the Icahn School of Medicine at Mount Sinai, presented the Jan. 13 Keystone Science Lecture Seminar Series talk at NIEHS. Hosted by William Suk, Ph.D., director of the NIEHS Superfund Research Program (SRP), Arora discussed his research on “Uncovering Early Life Exposure to Chemical Mixtures Using Micro-spatial Analysis of Teeth.”

“A good way to think of this research is to consider teeth as an encrypted hard drive,” said Arora. “We are trying to break down that encryption and look at different layers of information on each tooth. Some layers give us information on environmental pollutants, others on diet. And I believe there are many more layers of information to uncover.”

Understanding critical developmental windows

Although studies are making progress in better understanding the timing of exposures, Arora pointed out the difficulty of using prospective studies to link exposures to outcomes.

“For an outcome that affects one in 100, you would need about 10,000 mother-child pairs to get a sample size of close to 100 in a prospective study. One way to avoid this is to match cases to controls and look retrospectively, but then we have to reconstruct exposures leading up to the health outcome,” said Arora. “Using maternal biological markers doesn’t always accurately reflect fetal exposure, since different chemicals cross the placenta at different levels. This is where teeth come in.”

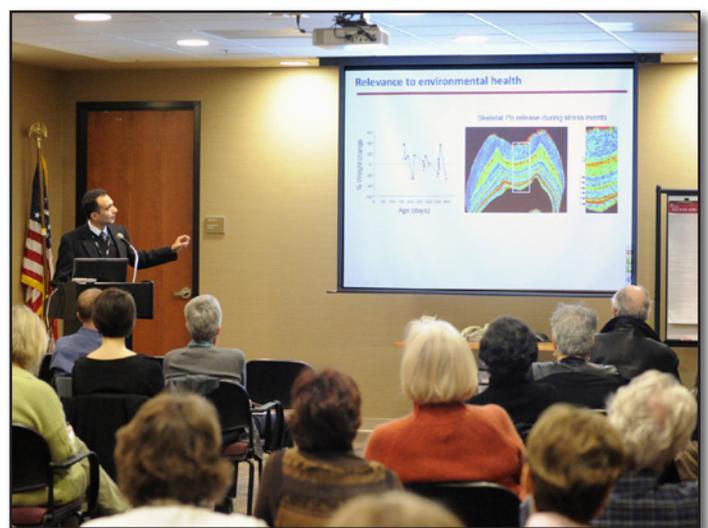


Arora is an assistant professor of preventive medicine and dentistry, and director of exposure biology at the Icahn School of Medicine at Mount Sinai. He is an NIEHS grantee and former postdoctoral trainee at the Harvard University SRP Center. (Photo courtesy of Steve McCaw)

 [Listen as Arora describes how much information can be found by analyzing teeth. \(0:57\)](#)

 [Read Transcript](#)

Teeth start developing prenatally and carry an imprint of daily circadian rhythm, the body’s internal clock. During development of a tooth, rings are formed, much like the rings of a tree. Arora’s research team has developed methodology that combines detailed analysis of the layers of teeth that correspond to specific life stages. They can use this information to reconstruct exposure to individual chemicals and chemical mixtures, as well as cumulative exposure, in the second and third trimesters of prenatal development and early childhood.



Arora explained how mapping homeostatic disruption, the disruption of the body’s internal equilibrium, in teeth can provide insight into response to environmental exposures during different developmental windows. (Photo courtesy of Steve McCaw)

Samples for these early-life exposure studies can be collected non-invasively, because most children lose their baby teeth between the ages of 6 and 13.

Linking innovative research to NIEHS priorities

Arora is particularly interested in exploring how we respond to environmental mixtures, an NIEHS priority described in a 2013 Environmental Health Perspectives [editorial](#).

In his work using children's teeth to map early-life exposure in cohorts in Mexico and the U.S., Arora is working to better understand how chemical mixtures affect children differently. Looking at more than 10 chemicals across 50 developmental time points per individual, Arora's research team is revealing potential critical windows of susceptibility to chemical mixtures.

They are also investigating how disruptive conditions, such as stress, can change the way chemical exposures affect the body, and working toward understanding the pathways involved in disruption of normal body functions as a result of chemical, physical, and psychological stressors.

“In the past, the field of environmental health has focused on measuring exposures and linking that to an outcome, but that approach misses information about how different people respond to different exposures,” said Arora. “We are looking at toxicant interactions more closely, by examining the disruptions of different pathways after exposure, based on chemical signatures in teeth.”

Arora touched on some of his recent innovative findings related to chemical distributions in teeth, such as a May 2013 [study](#) published in the journal Nature.

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

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Webinar highlights new insights about childhood leukemia

By Audrey Pinto

In a webcast seminar (webinar) Jan. 8, two NIEHS-funded scientists from the University of California, Berkeley — physician epidemiologist [Catherine Metayer, M.D., Ph.D.](#), and exposure biologist [Stephen Rappaport, Ph.D.](#) — presented new findings from their ongoing research at the [Center for Integrative Research on Childhood Leukemia and the Environment \(CIRCLE\)](#).

Metayer addressed “Paternal and Maternal Tobacco Smoking and the Risk of Leukemia in Children,” and Rappaport explored “Using Newborn Dried Blood Spots to Estimate *In Utero* Exposures to Chemicals.” Their presentations were part of the [Children's Centers 2014 Webinar Series](#) sponsored by NIEHS and the U.S. Environmental Protection Agency.

Linking father's tobacco smoking and childhood leukemia

Metayer's research focuses on how exposure to contaminants in the womb and in early life contribute to acute lymphocytic leukemia ([ALL](#)), the most common cancer among children.

To identify the causes of this disease, she and her research team are using data on almost 1,000 childhood leukemia cases from the NIEHS-sponsored California Childhood Leukemia Study (CCLS) to analyze associations between household environmental exposures and childhood leukemia. As she explained, “Access to this extensive database places the research teams at the CIRCLE in a unique position to disentangle the relationships between chemical exposures and childhood leukemia.”

Using this data has led Metayer’s team to target a risk factor that has recently attracted attention in several studies worldwide — active tobacco smoking by the father. Tobacco smoke contains several carcinogens and is known to also damage germ cells in sperm. Referring to what is known as the two-hit model hypothesis for leukemogenesis — the induction or production of leukemia — Metayer said there is increasing evidence that exposures to the father’s active smoking before or around conception, and to secondhand smoke after birth, are two necessary steps leading to an increased risk of specific types of childhood ALL.

Tobacco smoking appears to also increase the risk of acute myeloid leukemia in children, a relationship that is already well established among adults. [Metayer reported](#), however, that the CCLS and other studies do not find an association between reported active tobacco smoking by the mother during pregnancy, and childhood leukemia. This observation remains poorly understood.

Metayer concluded her presentation by calling for the additional research needed to replicate the findings; identify critical, time-specific windows of exposure; and investigate the role of genetic susceptibility. More analyses are underway within the [Childhood Leukemia International Consortium](#), which assembles data for thousands of children with leukemia around the world.

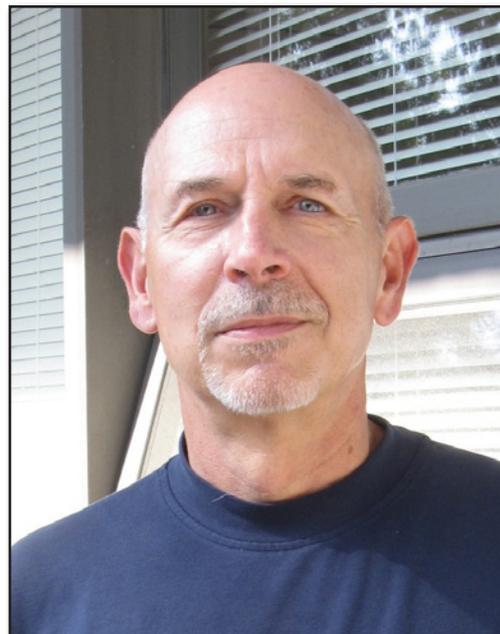
A new approach to measuring early life environmental exposures

Rappaport is a pioneer in the emerging fields of exposure biology and exposomics, and in the use of blood protein adducts as biomarkers of exposure to toxic chemicals.

In his presentation, Rappaport described his analysis of adduct populations to identify possible biomarkers of childhood leukemia and chronic diseases. His ultimate objective is to design a stable and consistent process that can characterize the totality of a person’s environmental exposures, and identify evidence of exposures to chemicals before birth.



“There are many reasons why we are interested in understanding the relationship between tobacco smoking and cancer in children,” Metayer said. (Photo courtesy of Catherine Metayer)



“We still have a lot to do,” Rappaport said of his untargeted and targeted omics studies. “This is really the first step.” (Photo courtesy of Stephen Rappaport)

Measuring adducts in neonatal dried blood spots

Using neonatal dried blood spots (DBS), which are available to the CCLS from the State of California, Rappaport's laboratory developed an assay to purify the blood protein, human serum albumin (HSA), and measure adducts of HSA produced by particular chemicals. Such HSA adducts in DBS reflect exposures during the last month of pregnancy.

The adducts Rappaport selected for his pilot study are related to chemicals in cigarette smoke.

To identify evidence of exposures to smoke-related chemicals before birth, he measured the HSA adducts in DBS from children of smoking and nonsmoking mothers. His preliminary findings indicate that some of the targeted HSA adducts were present at higher levels in children of smoking mothers.

In his conclusion, Rappaport explained that DBS offer a valuable tool for identifying fetal exposures. He noted that DBS from the State of California are particularly valuable for this purpose, because they are archived at minus 20 degrees Celsius, a temperature that protects HSA and the associated adducts from degradation.

Unfortunately, most other states do not preserve neonatal DBS in this manner. When stored at room temperature, adducts may not be stable for longer than about 6 months.

Citations:

Metayer C, Zhang L, Wiemels JL, Bartley K, Schiffman J, Ma X, Aldrich MC, Chang JS, Selvin S, Fu CH, Ducore J, Smith MT, Buffler PA. 2013. Tobacco smoke exposure and the risk of childhood acute lymphoblastic and myeloid leukemias by cytogenetic subtype *Cancer Epidemiol Biomarkers Prev* 22(9):1600-1611.

Metayer C, Milne E, Clavel J, Infante-Rivard C, Petridou E, Taylor M, Schuz J, Spector LG, Dockerty JD, Magnani C, Pombo-de-Oliveira MS, Sinnett D, Murphy M, Roman E, Monge P, Ezzat S, Mueller BA, Scheurer ME, Armstrong BK, Birch J, Kaatsch P, Koifman S, Lightfoot T, Bhatti P, Bondy ML, Rudant J, O'Neill K, Miligi L, Dessypris N, Kang AY, Buffler PA. 2013. The Childhood Leukemia International Consortium. *Cancer Epidemiol* 37(3):336-347.

Rappaport SM, Li H, Grigoryan H, Funk WE, Williams ER. 2012. Adductomics: characterizing exposures to reactive electrophiles. *Toxicol Lett.* 213(1):83-90.

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

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Leukemia and children's health

According to Metayer and Rappaport, childhood leukemia is a major public health issue that deserves much more interdisciplinary research support.

Between 1975 and 2004, the incidence of ALL, which accounts for most childhood leukemias in countries in the Western Hemisphere, rose significantly in the United States, Europe, and Japan, yet the causes of 90 percent of childhood leukemias are unknown.

For more than forty years, studies have demonstrated the toxicity of tobacco smoking. Contrary to what one would expect, however, most have failed to find a definitive link between maternal tobacco smoking before and after birth, and the risk of leukemia in children. Even less is known about other environmental and genetic factors that may contribute to the disease.

Talk explores link between endometriosis and the estrogen receptor

By Monica Frazier

A meeting of the NIEHS Receptor Mechanisms Discussion Group Jan. 7 featured a seminar by postdoctoral fellow [Katherine Burns, Ph.D.](#), of the Receptor Biology Group (RBG) on “The Role of Estrogen Receptor Signaling in Endometriosis.”

Seminar host [Kenneth Korach, Ph.D.](#), lead researcher in RBG and head of the NIEHS Laboratory of Reproductive and Developmental Toxicology, opened the meeting by discussing the history of the Receptor Mechanisms Discussion Group, established more than thirty years ago, and the contributions Burns has made to RBG through her passion for endometriosis research.

Burns began her presentation by noting some eye-opening facts about endometriosis, which affects approximately 5.5 million women in the U.S. and costs the country some \$22 billion annually. In addition to its prevalence and cost, the need to establish an understanding of endometriosis progression is driven by the lack of clinical biomarkers. Presently, endometriosis can be diagnosed only through laparoscopic surgery.

Burns added that for many years the disease has been thought to be associated with estrogen and possibly estrogen-like chemicals in the environment, but there is little research to prove the connection — something she is trying to change.

Developing an endometriosis disease model

An initial hurdle that Burns overcame was to find a good model for studying endometriosis, a condition where cells from the uterus flourish outside the uterine cavity. A condition, known as retrograde menstruation, allows endometrial debris to exit the uterus through the fallopian tubes. This backward movement of menstrual fluid through the fallopian tubes into the abdominal cavity is the leading hypothesis for the formation of endometriosis lesions.

Interestingly, although Burns noted that retrograde menstruation occurs in greater than 90 percent of women, only about 10 percent develop endometriosis. However, she said, through the development of a disease model, “We may be able to study the early initiation of this disease and potentially understand how and why it is forming in some women and not others.”

To study the potential role of estrogen receptors (ER) in the development of endometriosis lesions, Burns used both donor and host mice that have one of the genes for ER alpha or beta knocked-out. From her mouse studies, Burns developed a working



Burns, a guest speaker at the January Receptor Mechanisms Discussion Group, explained her research on the estrogen receptor's role in endometriosis to an audience of scientists involved in receptor signaling research. (Photo courtesy of Steve McCaw)



Hong Soon Kang, Ph.D., staff scientist in the NIEHS Cell Biology Group, listened during the question and answer session after Burns' seminar. (Photo courtesy of Steve McCaw)

endometriosis model, to recapitulate human disease and find lesions that are essentially indistinguishable from human lesions, that illustrates the role of ER alpha and beta in lesion establishment and progression.

Environmental exposures and endometriosis

Now that Burns has a working model of disease initiation and progression, she is beginning to look at how environmental toxicants, such as bisphenol A (BPA), may affect endometriosis. Since BPA and the fluorinated variant of BPA, BPAF, have estrogenic-like activity, Burns suspects they play a role in endometriosis and other reproductive conditions.

Burns' initial experiments show that BPA and BPAF have effects on the uterus similar to doses of estrogen, but the BPAF effect is stronger.

“We predict that BPAF may potentiate the development of endometriosis,” Burns commented, noting that she intends to continue to study this relationship in future experiments.

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

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This month in EHP

The February issue of [Environmental Health Perspectives \(EHP\)](#) highlights the health impacts on the Navajo population of uranium mining, and radioactive consequences of fracking.

Once Upon a Mine: The Legacy of Uranium on the Navajo Nation

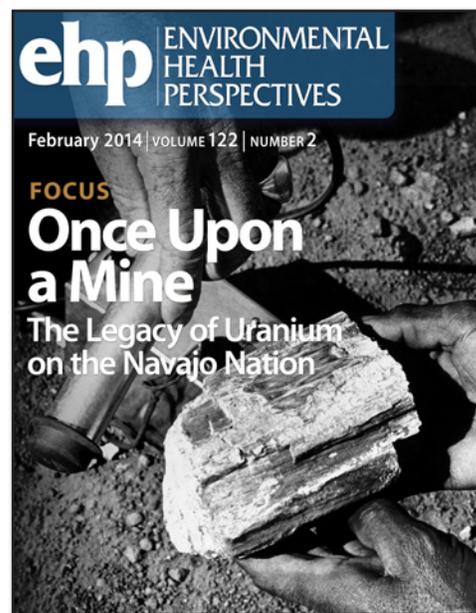
The Navajo Nation is home to hundreds of abandoned uranium mines, ranging from small holes dug by a single prospector into the side of a mesa, to large commercial mining operations. Within decades of the arrival of prospectors in the 1940s, Navajo miners were developing lung cancer, a relatively rare disease in this largely nonsmoking population. Today the Navajo population remains at high risk for kidney disease as a result of uranium exposure, as well as potentially associated hypertension, cardiovascular disease, and autoimmune diseases.

Radionuclides in Fracking Wastewater: Managing a Toxic Blend

Extracting gas from the multi-state Marcellus Shale Formation usually entails a practice known as hydraulic fracturing (fracking). Fracking brings up more than gas from the depths — the wastewater that flows to the surface contains radioactive materials that must be managed and disposed of. Fracking in the Marcellus has advanced so quickly that public understanding and research on its radioactive consequences have lagged behind, and there are many questions about the extent and magnitude of the potential risk to human health.



<http://twitter.com/ehponline>



Featured research and related news articles this month include:

- **F2RL3 Methylation as a Biomarker of Current and Lifetime Smoking Exposures** — A Smoking Gun? Epigenetic Markers of Tobacco Use History
- **Evaluating the Effectiveness of Fish Consumption Advisories: Modeling Prenatal, Postnatal, and Childhood Exposures to Persistent Organic Pollutants** — Fish Consumption Caveat: Advisories May Not Help With Long-Lived Contaminants
- **Environmental Noise Pollution in the United States: Developing an Effective Public Health Response** — Fighting Noise Pollution: A Public Health Strategy
- **Polyfluoroalkyl Chemicals and Menopause Among Women 20-65 Years of Age (NHANES)** — PFCs and Early Menopause: Association Raises Questions About Causality

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Myles Brown to give distinguished lecture

By Shannon Whirledge

The second NIEHS distinguished lecture of 2014 will be presented Feb. 11 by prominent physician scientist [Myles Brown, M.D.](#), at 11:00 a.m. in Rodbell Auditorium. NIEHS Reproductive and Developmental Toxicology Laboratory head [Kenneth Korach, Ph.D.](#), will host Brown's talk, "Genetics and Epigenetics of Endocrine Resistance."

Brown is a professor of medicine at Harvard Medical School and director of the Center for Functional Cancer Epigenetics at the Dana-Farber Cancer Institute. The Brown laboratory at Harvard Medical School focuses on elucidating the epigenetic factors underlying steroid hormone action, with implications for both normal physiology and the treatment of hormone-dependent cancer.

Brown is widely recognized for several important discoveries in the steroid receptor field. His group's research has shed light on the complex nature of steroid receptor coregulators, including the dynamic nature of receptor and coregulator interactions with the genome. Some recent findings from Brown's group highlight the ability of epigenetic modifications to dictate transcription factor binding to discrete regulatory regions in the mammalian genome.

Among his many accomplishments, Brown has published more than 150 peer-reviewed articles, reviews, and book chapters that have been highly quoted, and he has been invited to present lectures at conferences worldwide. His many honors include being elected to the American Society for Clinical Investigation in 1997 and the Association of American Physicians in 2003, receiving the Tisch Family Outstanding Achievement Award in 2006, and being presented the Edwin B. Astwood Award by The Endocrine Society in 2010.



Brown is a pioneer in the field of cancer research. His seminal discoveries include the first identification of the p160 class of steroid receptor coactivators and the description of the estrogen receptor cistrome, the targets of estrogen action across the genome. His work has important implications for understanding the actions of selective receptor modulators and endocrine disruptors. (Photo courtesy of Myles Brown)

Researchers at NIEHS and in the local community are enthusiastic to have Brown present his studies on a current and relevant topic. As Korach said, “Dr. Brown’s research in the field of hormone action and nuclear receptor mechanisms in breast cancer is highly relevant to studies at the NIEHS involving environmental endocrine-disrupting chemicals.”

(Shannon Whirlledge, Ph.D., is an Intramural Research Training Award fellow in the NIEHS Molecular Endocrinology Group.)

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Extramural papers of the month

By *Nancy Lamontagne*

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Read the current Superfund Research Program [Research Brief](#). New issues are published on the first Wednesday of each month.

Transcription factor influences codon choice and protein evolution

Research, partially supported by an NIEHS grant funded by the National Institutes of Health Common Fund, revealed that complex genomes simultaneously code for amino acids and regulatory information. The work adds a transcription factor binding code to the spectrum of other regulatory codes that are believed to influence protein evolution by influencing codon choice.

Genomes contain protein-coding regions, as well as regulatory code that influences gene expression by specifying recognition sequences for transcription factors. Scientists have assumed that the genetic code and regulatory codes were physically and operationally independent. To find out if these codes intersect, the researchers created a nucleotide-resolution map showing where protein-coding regions of the human genome were occupied by a transcription factor. They looked at 81 diverse cell types, and found that approximately 15 percent of human codons simultaneously specify both proteins and transcription factor recognition sites. These dual-use codons, or duons, are highly conserved, and constraint from the transcription factors appears to be a major driver of codon usage bias. The researchers found that more than 17 percent of single-nucleotide variants within duons directly altered transcription factor binding.

The researchers concluded that widespread dual encoding of amino acid and regulatory information appears to be a fundamental feature of genome evolution.

Citation: [Stergachis AB, Haugen E, Shafer A, Fu W, Vernot B, Reynolds A, Raubitschek A, Ziegler S, LeProust EM, Akey JM, Stamatoyannopoulos JA. 2013. Exonic transcription factor binding directs codon choice and affects protein evolution. Science 342\(6164\):1367-1372.](#)

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Compound from mold linked to symptoms of Parkinson's disease

NIEHS grantees report that an organic compound emitted by mold might be linked to Parkinson's and other neurodegenerative diseases in humans. Studies have found evidence that several environmental agents, especially pesticides, are possible risk factors for Parkinson's disease, but this is the first naturally occurring environmental agent identified as a potential risk factor.

Exposure to fungi has been linked to movement disorders, as well as loss of balance and coordination, but the mechanisms involved in these health effects are unknown. To find out more about the possible toxicological effects of fungal volatile organic compounds associated with indoor environments, the researchers screened a variety of fungal toxicants using fruit flies. The volatile fungal semiochemical 1-octen-3-ol emerged as one of the most potent agents they tested. 1-octen-3-ol is commonly emitted by molds and is responsible for much of the moldy odor associated with fungal colonization.

Parkinson's disease is associated with the loss of neurons that produce the neurotransmitter dopamine. The researchers found that low levels of 1-octen-3-ol reduced dopamine levels and caused dopamine neuron degeneration in the fruit flies. Genetic and cell culture studies revealed that 1-octen-3-ol most likely exerts toxicity by disrupting dopamine handling. The agent also increased loss of dopaminergic neurons through interactions with genetic variants of the vesicular monoamine transporter, which is involved in dopamine biosynthesis.

Citation: [Inamdar AA](#), [Hossain MM](#), [Bernstein AI](#), [Miller GW](#), [Richardson JR](#), [Bennett JW](#). 2013. Fungal-derived semiochemical 1-octen-3-ol disrupts dopamine packaging and causes neurodegeneration. *Proc Natl Acad Sci U S A* 110(48):19561-19566.

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New tool for assessing ovarian cancer

An NIEHS grantee and colleagues developed a new technique that may help predict ovarian treatment response, cancer recurrence, and disease-free survival earlier and more effectively than current methods.

For many types of cancer, counting the number of tumor-attacking immune cells (TILs) that have migrated into the tumor offers a way to predict a patient's survival. The number of TILs indicate the body's immune response to the cancer, but current methods for counting TILs are either technically challenging or exhibit too much variability to be used for clinical decisions. The new approach, which the researchers call QuanTILfy, uses droplet digital polymerase chain reaction technology to count TILs reliably, quickly, and cheaply.

The researchers tested QuanTILfy on tumor samples from 30 ovarian cancer patients who had survival times ranging from one to 22 months. The results showed an association between higher TIL counts and improved survival among women with ovarian cancer, which was consistent with other studies that had found that a person's immune response against ovarian cancer can be used to estimate survival.

The ability to reproducibly compute TILs in tumors with sensitivity may allow doctors to stratify and more effectively treat patients based on tumor TIL counts.

Citation: [Robins HS](#), [Ericson NG](#), [Guenthoer J](#), [O'Briant KC](#), [Tewari M](#), [Drescher CW](#), [Bielas JH](#). 2013. Digital genomic quantification of tumor-infiltrating lymphocytes. *Sci Transl Med*. 5(214):214ra169.

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Partnership identifies chemical-gene-disease interactions for inclusion in database

Environmental health researchers and pharmaceutical drug developers share the common goal of improving the ability to predict chemical toxicity. With this goal in mind, Pfizer safety scientists and the biocuration staff at the [Comparative Toxicogenomics Database \(CTD\)](#) collaborated in text mining and manually reviewing more than 88,000 scientific articles, to develop a dataset of adverse events from drugs. Funded in part by NIEHS, this partnership demonstrates the benefits of resource sharing and collaboration between public and private entities with complementary needs.

CTD is a public database that promotes understanding about how the molecular interactions between environmental chemicals and genes affect human health. CTD curators use text mining and manual curation to convert knowledge from scientific papers into data on chemical-gene, chemical-disease, and gene-disease interactions that can be more easily managed, queried, explored, and analyzed. The collaborating researchers text mined and manually reviewed 88,629 articles with information on the potential involvement of 1,200 pharmaceutical drugs in cardiovascular, neurological, renal, and hepatic toxicity. In one year, this process produced 254,173 toxicogenomic interactions, including 152,173 chemical-disease, 58,572 chemical-gene, 5,345 gene-disease, and 38,083 phenotype interactions. All of these interactions are fully integrated into the public CTD.

Citation: [Davis AP, Wieggers TC, Roberts PM, King BL, Lay JM, Lennon-Hopkins K, Sciaky D, Johnson R, Keating H, Greene N, Hernandez R, McConnell KJ, Enayetallah AE, Mattingly CJ. 2013. A CTD-Pfizer collaboration: manual curation of 88,000 scientific articles text mined for drug-disease and drug-phenotype interactions. Database \(Oxford\) 2013:bat080. \[Story\]](#)

(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 Kelly Lenox, Kristin Lichti-Kaiser, Mallikarjuna Metukuri, and Zack McCaw

- [Scientists closer to understanding stem cell self-renewal and differentiation](#)
- [Estrogen receptor alpha involved in DES-induced gene expression in male mice](#)
- [Identification of a novel mechanism that suppresses glucocorticoid signaling](#)
- [Factors critical during early stages of heart development clarified](#)

Scientists closer to understanding stem cell self-renewal and differentiation

A research team, led by NIEHS scientists, determined that the mRNA export complex THO, present in embryonic stem cells (ESCs), preferentially interacts with and regulates pluripotency gene expression.

Pluripotency is the ability of a cell to develop into any type of cell, and self-renewal is the ability of a cell to proliferate while maintaining its developmental potential. ESCs that lack Thoc5 or Thoc2, two components of THO, lose this self-renewal capacity and differentiate into various cell types. This research is vitally important to basic and clinical research because scientists use ESCs to derive cells for disease modeling, drug discovery, and the development of cell-based therapies.

The authors cultured ESCs and transfected cells with either Thoc2 or Thoc5 small interfering RNAs (siRNAs) in 96-well plates. Other experimental techniques included immunofluorescence, microarray, and RNA immunoprecipitation and sequencing.

The researchers found that THO, via Thoc5, is needed for ESC self-renewal. Furthermore, they discovered that a decrease of THO inhibited somatic cell reprogramming and blastocyst development, making THO a required complex in the establishment of pluripotency. The finding that ESC self-renewal and differentiation occurs at the post-transcriptional level brings scientists closer to understanding the mechanisms involved in stem cell fate specification. **(ZM)**

Citation: Wang L, Miao YL, Zheng X, Lackford B, Zhou B, Han L, Yao C, Ward JM, Burkholder A, Lipchina I, Fargo DC, Hochedlinger K, Shi Y, Williams CJ, Hu G. 2013. The THO complex regulates pluripotency gene mRNA export and controls embryonic stem cell self-renewal and somatic cell reprogramming. *Cell Stem Cell* 13(6):676-690. [[Story](#)]

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Estrogen receptor alpha involved in DES-induced gene expression in male mice

In a recent issue of *Environmental Health Perspectives*, NIEHS researchers are the first to report a novel estrogen receptor alpha (ERalpha) dependent correlation between DNA methylation patterns and levels of the *Svs4* and *Ltf* genes, after neonatal diethylstilbestrol (DES) exposure in male mice. This work provides more detail on the negative effects of endocrine-disrupting chemicals on mammals.

Researchers used a neonatal DES exposure mouse model to examine changes in the methylation patterns of androgen-dependent gene *Svs4* and estrogen-dependent gene *Ltf* in the seminal vesicles of male mice. They found that DNA methylation of the *Svs4* gene promoter changed from methylated to unmethylated during development, and that DES exposure prevented this change. In the *Ltf* gene promoter, DES exposure altered the methylation status from methylated to unmethylated at two specific CpGs. Alterations in methylation status correlated with decreased levels of *Svs4* and increased levels of *Ltf* gene expression in an ERalpha-dependent manner. In addition, DES exposure increased expression of epigenetic modifiers. **(KLK)**

Citation: Li Y, Hamilton KJ, Lai AY, Burns KA, Li L, Wade PA, Korach KS. 2013. Diethylstilbestrol (DES)-stimulated hormonal toxicity is mediated by ERalpha alteration of target gene methylation patterns and epigenetic modifiers (DNMT3A, MBD2, and HDAC2) in the mouse seminal vesicle. *Environ Health Perspect*; doi:10.1289/ehp.1307351 [Online 6 December 2013].

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Identification of a novel mechanism that suppresses glucocorticoid signaling

A recent study conducted by researchers at NIEHS identified hairy and enhancer of split-1 (HES1) as a novel regulator of glucocorticoids, the primary stress hormones essential for life. HES1 is a key regulator of development and organogenesis, and the authors suggest abnormal expression of HES1 may contribute to forms of glucocorticoid resistance seen in some patients.

The authors demonstrated that glucocorticoids silence HES1 gene and protein expression in multiple cell types and tissues. Overexpression of HES1 in human cells led to reduced glucocorticoid-mediated changes in gene expression and vice versa. In addition, a mutated form of HES1 could not impair glucocorticoid signaling. To assess the effects *in vivo*, the authors generated HES1 liver knockout mice, which displayed abnormal glucocorticoid-dependent signaling profiles that resulted in impaired glucose tolerance. This metabolic phenotype was corrected by the removal of endogenous glucocorticoids by adrenalectomy, whereas injection of exogenous glucocorticoids restored it.

The findings suggest that the dismissal of HES1 cooperates with the glucocorticoid receptor to regulate a large component of the transcriptional targets of glucocorticoids through a transcriptional derepression mechanism. The authors propose that HES1 is a master regulator of glucocorticoid signaling profile and silencing of HES1 is required for proper glucocorticoid signaling. **(MM)**

Citation: [Revollo JR, Oakley RH, Lu NZ, Kadmiel M, Gandhavadi M, Cidlowski JA](#). 2013. HES1 is a master regulator of glucocorticoid receptor-dependent gene expression. *Sci Signal* 6(304):ra103.

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Factors critical during early stages of heart development clarified

NIEHS researchers studying heart development in mammalian embryos reported several important findings that reveal specialized and novel cardiac-enriched Switch/Sucrose NonFermentable (SWI/SNF) chromatin-remodeling complexes. Because these complexes are required for heart formation and critical for cardiac gene expression regulation at the early stages of heart development, the results will be valuable in improving cardiac reprogramming strategies and elucidating the mechanisms that contribute to congenital heart disease.

Studying mouse embryos at distinct developmental stages, researchers demonstrated that the SWI/SNF complex subunits exhibit differential patterns of expression in early development, and that specific BRG1-associated factors were elevated in the early heart compared with head and trunk. Subsequent studies revealed that the BAF250a subunit was required for fully functional cardiomyocyte differentiation *in vitro*. Results suggest that the subunit BAF250a plays a regulatory role in early heart formation, via the direct repression of cardiac-specific gene expression. Molecular analyses suggest that BAF250a physically interacts with repressor proteins, including CHD4 and HDAC1, to alter the chromatin architecture and epigenetic signature of cardiac related genes.

Defining a previously unknown SWI/SNF complex composition and spatiotemporal expression pattern, these findings provide novel insight into the role of the complex in cardiac lineage decision and subsequent heart formation during early development. **(KL)**

Citation: [Singh AP, Archer TK](#). 2013. Analysis of the SWI/SNF chromatin-remodeling complex during early heart development and BAF250a repression cardiac gene transcription during P19 cell differentiation. *Nucleic Acids Res*; doi:10.1093/nar/gkt1232 [Online 13 December 2013].

(Kelly Lenox is editor of the Environmental Factor. Kristin Lichti-Kaiser, Ph.D., is an Intramural Research Training Award (IRTA) fellow in the NIEHS Cell Biology Group. Mallikarjuna Metukuri, Ph.D., is a research fellow in the NIEHS Metabolism, Genes, and Environment Group. Zachary McCaw is a postbaccalaureate IRTA fellow in the NIEHS Environmental Genetics Group.)

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Inside the Institute

NIEHS CFC raises more than \$100,000

By Allison Eason

Since 1961, the goal of the Combined Federal Campaign (CFC) has been to provide an opportunity for federal employees to give back to their communities. This year was no different, as NIEHS employees stepped up to raise \$100,425. The charitable drive was busier than ever, with a talent show, bake off, bake sale, silent auction, fun run, and yoga classes.



Staff from the Division of Extramural Research and Training led the NIEHS campaign. This year's co-chairs were Elizabeth Ruben of the Program Analysis Branch, Barbara Gittleman of the Grants Management Branch, and Danielle Carlin, Ph.D., of the Hazardous Substances Research Branch.

“We reached 87 percent of our goal, and we were honored to experience the generosity of NIEHSers,” said Ruben. “This year’s talent show was very well attended and provided a way for NIEHSers to connect and enjoy community spirit.”

Drive extended due to shutdown

The CFC takes place every year from October to December. Due to the government shutdown, the 2013 campaign was extended to Jan. 15. With nearly 3,000 charities accepting donations, a simple process made pledging easy for employees. Most chose to donate through online payroll deduction.

As part of the drive, several charities came to NIEHS Nov. 19, 2013, to give 2-minute presentations on their missions and goals, sharing how they help the less fortunate by providing support to those in need. The presentations were webcast in order to reach as many employees as possible.

The National Institutes of Health (NIH), of which NIEHS is part, exceeded its original goal during this year’s campaign. NIH Director Francis Collins, M.D., Ph.D., wrote, “With your generosity, and despite the unique challenge of the government shutdown, we met more than 100 percent of our \$2.2 million goal.”

Rising above economic challenges

The Greater N.C. Area CFC reported that donations totaled more than \$1.3 million. Even though there were spending cuts, a government shutdown, and economic stresses, the campaign still



*Ruben was proud to serve as a CFC co-chair.
(Photo courtesy of Steve McCaw)*



*“Helping those less fortunate is a life-guiding principle,” said CFC co-chair Gittleman.
(Photo courtesy of Steve McCaw)*

managed to fundraise at a remarkable level. The state’s CFC representatives Gina Misasi-Wood and Linda Matich Lang played a key role in leading the ambitious endeavor.

In an all-hands email, NIEHS and NTP Director Linda Birnbaum, Ph.D., thanked employees for supporting the many CFC events, and for being generous and caring. “The charities of your choice will now have resources in 2014 to deliver services to those in need.” Birnbaum also thanked the organizers of this year’s campaign for giving their time to plan the various promotions, activities, and events.

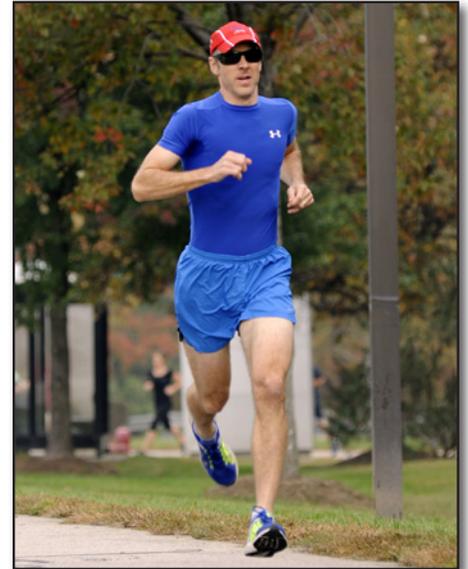
(Allison Eason is a program specialist in the NIEHS Office of Communications and Public Liaison.)



“Getting involved with the CFC lets you know that there’s a lot going on in our community,” Carlin added. (Photo courtesy of Steve McCaw)



Dick Sloane of the NIEHS Office of Management showcased his comical talents at the CFC talent show held Nov. 4, 2013. (Photo courtesy of Steve McCaw)



NIEHS Program Analyst Liam O’Fallon raced toward the finish line at this year’s popular CFC Fun Run. (Photo courtesy of Steve McCaw)

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NIEHS inaugurates new facilities for fitness, research, and training

By Kelly Lenox

A lively gathering of NIEHS staff kicked off the new year at a Jan. 8 open house for newly remodeled space in the main building. NIEHS and NTP Director Linda Birnbaum, Ph.D., opened with a few brief words.

“The whole objective [of the remodel] was to get us more usable, more functional space that we would all live in and enjoy,” she explained.

The new area includes a library, expanded fitness center, new training room, work/life office, and the Bioinformatics Team.

Bigger and better — and still free

Program manager Stephanie Bullock-Allen enthusiastically showed off the fitness facilities, encouraging employees to sign up for access, register for recreational sports teams, and pick up a calendar of classes. A raffle kept the curious streaming in.

At more than 2 1/2 times the size of the old space, the fitness center, both convenient and free, has a variety of fitness equipment, as well as plenty of room for exercise classes.

The best for work and life

A new work/life office accommodates a career counselor, Gordon Folger, and the NIH ombudsman, when on site. Keeping with the fitness theme, Folger handed out surveys to determine whether staff were keeping careers fit, too.

Bioinformatics team united

David Fargo, Ph.D., director of Integrative Bioinformatics, is pleased that the group is finally gathered in one place. The new workspace is designed to facilitate teamwork, as the staff provides bioinformatics and computational support to NIEHS researchers.

Top-notch training room

Though no one minded the sun pouring in on that frigid day, Roy Reter of the Computer Technology Branch demonstrated the light-blocking blinds, designed to ease eyestrain on the laptops. Besides training, the audio and video equipment in the room also supports videoconferencing.

Partners in research

The NIEHS library team used the roadmap theme of their motto (see sidebar) to educate staff about their services.

“Now that there is so much information out there, we can help you navigate it, by providing help finding articles. Or, if you’re doing a literature search, we can help you decide which databases to use or which keywords to select, because many scientific databases use very specific vocabularies,” explained library manager Erin Knight. “We can save you time and frustration.”



Smoothie samples — and recipes — were on hand, whetting the palate of many, including raffle winners April Parker, left, and Leslie Lynch. (Photo courtesy of Steve McCaw)

“To ask why we need libraries at all, when there is so much information available elsewhere, is about as sensible as asking if roadmaps are necessary now that there are so many roads.”

— Jon Bing, J.D., professor of information technology law, University of Oslo



Ming-Lang Zhao, M.D., didn't let visitors keep him from his workout. (Photo courtesy of Steve McCaw)



Birnbaum, who minutes earlier told the crowd, "I look forward to seeing some of you down here, as one of my resolutions is to use this fitness center," wasted no time signing up with Bullock-Allen. (Photo courtesy of Steve McCaw)

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