



UPDATE

National Toxicology Program

U.S. Department of Health and Human Services

November 2013

Headquartered at the
National Institute of Environmental
Health Sciences • NIH-HHS

What's Inside:

Calendar

Bishop honored
by Environmental
Mutagenesis and
Genomics Society

NTP postdocs
recognized with
Society for Toxicologic
Pathology awards

NTP postdoc
takes top prize at
NCSOT meeting

NTP talk explores
zebrafish as a
vertebrate model in
toxicity screening

NIEHS holds high
throughput
toxicogenomics
platforms workshop

NIEHS and NTP
join colleagues at
Teratology Society
meeting

Talking
toxicogenomics and
global database

ICCVAM

Subscribe to the
NTP Listserv

NTP Publications and
Technical Reports

East meets west at international toxicology congress in Seoul

By Eddy Ball, reprinted from *eFACTOR*, August 2013

As one of global toxicology's leading figures, NIEHS and NTP Director Linda Birnbaum, Ph.D., presented a keynote lecture July 2, and chaired sessions, at an international meeting devoted to translational toxicology.

Birnbaum led the six-member U.S. National Toxicology Program (NTP) delegation to the [XIII International Congress of Toxicology 2013 \(ICT2013\)](#) June 30-July 4 in Seoul, South Korea, where they joined a number of NIEHS grantees who also made presentations. The U.S. NTP delegation participated in sessions on the development of high throughput screening-based predictive toxicology, by sharing advances in the U.S. interagency Toxicology in the 21st Century (Tox21) program.



Birnbaum developed a simple theme in her talk, but one whose implications challenge the foundations of contemporary biomedical research — "You Can't Change Your Genes, but You Can Change Your Environment."
(Photo courtesy of ICT2013)



The XIII International Congress of Toxicology
June 30(Sun)–July 4(Thu), 2013, COEX, Seoul, Korea
KEY DATES >> Deadline of the Abstract Submission : January 31, 2013
>> Deadline of the Early Registration : January 31, 2013
ICT2013 Secretariat Tel +82-2-557-8422 Fax +82-2-566-6087 Email ict@ict2013seoul.org www.ict2013seoul.org



NTP Associate Director John Bucher, Ph.D., second from left, and Birnbaum, to his right, co-chaired the session on "National Coordination of Toxicology Research and Testing" July 2. Lead NTP scientists Mary Wolfe, Ph.D., left, and Nigel Walker, Ph.D., right, also presented the U.S. perspective, while their Korean colleagues discussed their own initiatives in toxicology.
(Photo courtesy of Nigel Walker)

During the meeting, representatives of the U.S. NTP and Korean NTP also discussed international partnerships and participated in a meeting of the International Cooperation on Alternative Test Methods (ICATM). NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) Acting Director Warren Casey, Ph.D., represented the U.S. in discussions with colleagues from around the world (see [text box](#)).

Following their formal meeting in Seoul, Birnbaum and the USNTP delegation joined representatives of the Korean NTP July 5 for a one-day post-congress retreat to continue their discussions.

In a pre-congress meeting June 30, Birnbaum took advantage of an opportunity to meet individually with Her Royal Highness Princess Chulabhorn Mahidol of Thailand, a leading figure in promoting global public health research in Southeast Asia. NIEHS has a long history of partnerships and collaborations in the region, through its Superfund Research Program, and supports research projects there, including ones on e-waste recycling in China and Vietnam.

Continued on next page



The U.S. NTP delegation joined their Korean counterparts, during the historic meeting. Shown, center to right, are Birnbaum, in beige, Wolfe, Walker, and Bucher. Not shown: Casey and NTP scientist Jef French, Ph.D., who spoke about development and applications of the DO mouse model. (Photo courtesy of ICT2013)

Delivering a strong environmental public health message

Addressing an audience of toxicologists and health scientists from around the world, Birnbaum reminded her listeners of the important role environment plays in human health.

“Global environmental health matters, because noncommunicable diseases are major causes of death worldwide and underlie almost two-thirds of all global deaths,” she said. “Although all countries face epidemics of these diseases, low-income and middle-income countries, and the poorest and most vulnerable populations within them, are affected the most.”

Referring to the Global Burden of Disease Study 2010 published in [The Lancet](#) in 2012, Birnbaum delivered a litany of figures on global public health that underscored what she called a global imperative to create and implement effective prevention strategies. “At least 13 million deaths could be prevented, per year, by improving our environment,” she said.

In her review of environmental health research by NIEHS and NTP, Birnbaum discussed several emerging concepts. Among them were the developmental origins of adult disease, endocrine disruption, epigenetic modification of gene expression, mixtures, and nonmonotonic dose response to hormones and hormone-like chemicals.

The final part of Birnbaum’s presentation moved into a discussion of Tox21 and NIEHS initiatives in the area of global health. Listing the accomplishments of Tox21 during its first four years, she described the 1000 Genomes Project, a genetically diverse platform for high-throughput screening, for prioritizing suspect chemicals for advanced evaluation, and the Diversity Outbred (DO) mouse, a new population-based mouse model for identifying, characterizing, and quantifying hazard, by final-stage *in vivo* assessments of high-priority chemicals selected through high-throughput *in vitro* screening.

Continued on next page

Upcoming Events

December 2, 2013

10:30 a.m.-12:00 p.m.

The NIEHS-NCATS-UNC DREAM Toxicogenetics Challenge: Crowdsourcing Tox21 Qualitative High Throughput Screening Data

http://www.niehs.nih.gov/funding/assets/docs/toxicogenetics_challenge_seminar_508.pdf

December 12-13, 2013

Peer Review of Draft Report on Carcinogens Monographs for ortho-Toluidine and Pentachlorophenol

<http://ntp.niehs.nih.gov/go/38853>

April 16-18, 2014

NTP Board of Scientific Counselors

<http://ntp.niehs.nih.gov/go/165>

June 17-18, 2014

NTP Board of Scientific Counselors

<http://ntp.niehs.nih.gov/go/165>

September 16-17, 2014

Scientific Advisory Committee on Alternative Toxicological Methods (SACATM)

<http://ntp.niehs.nih.gov/go/32822>

All meetings are held at NIEHS unless otherwise noted:

Rodbell Auditorium
NIEHS

111 TW Alexander Drive
Research Triangle Park, NC

<http://ntp.niehs.nih.gov/go/calendar>



Birnbaum concluded with examples of the role of NIEHS as a citizen of the world, by pointing to the new strategic plan and ongoing global health initiatives. These included the Institute's leadership in the Global Alliance for Clean Cookstoves initiative; collaborations in research on arsenic in drinking water, such as ongoing work in Asia and the Americas; impacts of electronic waste exposure in China, Vietnam, and other developing countries; and the health impact of climate change.

Over the following three days, Birnbaum and the NTP delegation joined experts from the U.S., Asia, and Europe in the exploration of the most effective ways to achieve the congress mission of building a translational toxicology program that progresses from basic science, to clinical and environmental outcomes, to enhance global public health. ●

Promoting alternative testing on an international level

By Cathy Sprankle

Casey presented an update on NICEATM activities July 3 at a coordination meeting of ICATM, an international partnership that promotes the advancement of replacement, reduction, and refinement alternatives for animal testing. Casey co-chaired the session with Soon Young Han, Ph.D., director of the Toxicological Evaluation and Research Department at the National Institute of Food and Drug Safety Evaluation, part of the Korea Food and Drug Administration, who represented the Korean Centre for the Validation of Alternative Methods.

The ICATM coordination meeting in Seoul included updates from Europe, Japan, Korea, and the U.S. on their current test method evaluation and validation activities. Casey's update was titled "A New Strategic Direction for ICCVAM and NICEATM: Future Plans for the Validation and Acceptance of Alternative Test Methods in the United States." He discussed NICEATM activities supporting Tox21 and NICEATM collaborations to develop new models to identify skin sensitizers, substances with the potential to cause allergic contact dermatitis.

Finding replacements for animal testing, to identify potential skin sensitizers, was the major focus at the July ICATM meeting. However, member organization representatives also provided updates on studies of alternative test methods to identify potential eye irritants, carcinogens, and endocrine-active substances.

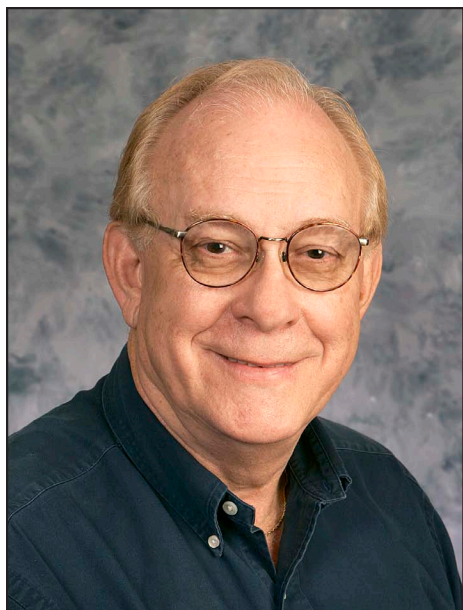
ICATM currently includes organizations from the European Union, U.S., Japan, Canada, and South Korea. The government of Brazil recently established the Brazilian Centre for the Validation of Alternative Methods (BraCVAM). The new center will begin participating in ICATM coordination meetings as an observer this fall.

ICATM coordination meetings take place several times a year and provide an opportunity for the five member organizations to discuss activities in the three critical areas of cooperation — validation studies, independent peer review of the validation of test methods, and the development of formal test method recommendations on alternative testing methods. The meetings are planned to coincide with meetings of the Society of Toxicology and other gatherings of mutual interest to the participant organizations. Regular interactions allow ICATM partners to develop good communications and working relationships, which support collaborations on test method development.

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

Bishop honored by Environmental Mutagenesis and Genomics Society

By Robin Arnette, reprinted from *eFACTOR*, October/November 2013



During his long association with EMGS, Bishop served as treasurer, executive board member, and past president of one of its regional groups. (Photo courtesy of Steve McCaw)

When former National Toxicology Program (NTP) geneticist Jack Bishop, Ph.D., retired in 2012, after 40 years of federal service, he had amassed an impressive record of scientific accomplishments, including more than 100 peer-reviewed journals articles, presentations at dozens of national and international conferences, and decades of experience in germ cell mutagenesis and environmental toxicology. Now, he has one more accolade to add to the list.

The [Environmental Mutagenesis and Genomics Society \(EMGS\)](#) named Bishop as its 2013 Alexander Hollaender Award winner. The EMGS is dedicated to promoting research that examines the causes and consequences of damage to the genome and epigenome. According to its website, the award is given each year in recognition of outstanding contributions in the application of the principles and techniques of environmental mutagenesis to the protection of human health.

Bishop received the award during the society's annual meeting September 24, in Monterey, Calif., and joins two other NIEHS award recipients. Former NTP toxicologist Mike Shelby, Ph.D., won in 1988, and Biomolecular Screening Branch chief Raymond Tice, Ph.D., received the honor in 2009.

"I am very humbled and honored to receive this award and to be included in such a prestigious list of Alexander Hollaender Award winners," Bishop said upon hearing the news.

Bishop came to NTP in 1985 from the U.S. Food and Drug Administration National Center for Toxicological Research in Jefferson, Ark., where he spent 10 years investigating chemically-induced mutagenesis in rodent germ cells. Prior to that, he was a research geneticist at the U.S. Department of Agriculture Bee Breeding and Stock Center Laboratory in Baton Rouge, La.

While at the NTP, he served in the [Toxicology Branch](#) as project officer for research that evaluated the reproductive and developmental toxicity of chemicals, and conducted his own studies in reproductive, developmental, and genetic toxicity. Bishop was also instrumental in the effort to develop biomarker assays for detecting genetic damage in rodent sperm, using fluorescence in situ hybridization.

Two examples of his work represent ground-breaking research in the field of environmental mutagenesis. His 2003 report found that the chemical agent N-hydroxymethylacrylamide had detrimental effects in mouse germ cells, or the cells involved in reproduction, rather than somatic cells, which comprise all of the other cells in an organism. Bishop also determined that pregnant women who took azidothymidine, a medication used to treat patients with HIV-AIDS, gave birth to children who sustained some genetic damage, as a result of the drug's ability to cross the placental barrier.

John Bucher, Ph.D., NTP associate director, said Bishop's commitment to research, organizing international workshops, and mentoring young scientists made him an outstanding candidate for the award.

"Jack has been instrumental in helping the NTP have a prominent and forward thinking role in the field of environmental mutagenesis," Bucher said. "NTP is fortunate to have had several NTP staff recognized by EMGS over the years." ●



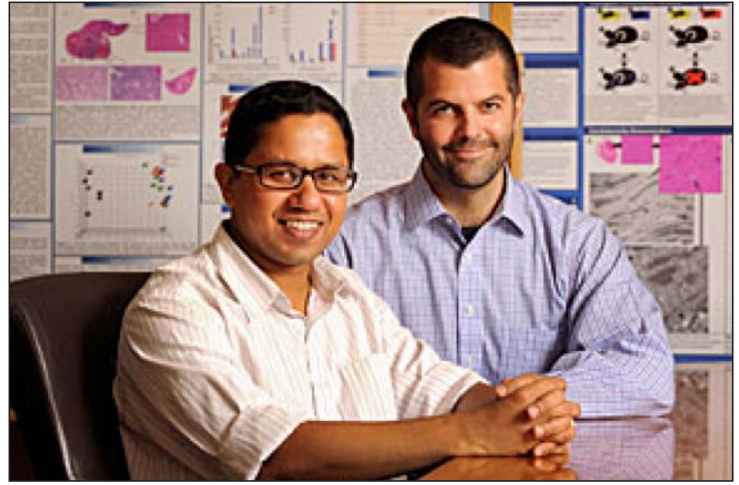
NTP postdocs recognized with Society for Toxicologic Pathology awards

By Eddy Ball, reprinted from *eFACTOR*, August 2013

NTP postdocs won two of the three Young Investigator Awards presented at this year's [Society of Toxicologic Pathology \(STP\) annual meeting](#) June 16-20 in Portland, Ore.

The NTP awardees are Sachin Bhusari, D.V.M., Ph.D., who placed first, and Michael Boyle, D.V.M., who placed third. Bhusari is a member of the Cellular and Molecular Pathology Branch (CMPB) Investigative Pathology Group, headed by pathologist Mark Hoenerhoff, D.V.M., Ph.D.

Boyle is part of the CMPB NTP Pathology Group, headed by pathologist David Malarkey, D.V.M., Ph.D., and is also being mentored in his Ph.D. research, on the modulation of chromatin-remodeling factors in cardiovascular development and disease, by NIEHS lead researcher Trevor Archer, Ph.D., head of the Laboratory of Molecular Carcinogenesis.



Bhusari, left, and Boyle were recognized by the world's leading professional organization in the advancement of pathology, as it pertains to changes elicited by pharmacological, chemical, or environmental agents, as well as factors that modify these responses. STP membership includes some 1,250 scientists and professionals in more than 28 countries. (Photo courtesy of Steve McCaw)

Kudos for the winners and for NTP

Both awardees earned high praise on the quality of their research and the impact that this research has on the scientific community (see [text box](#) in the *eFactor* [☞](#)) from their mentors, as well as from CMPB head Robert Sills, D.V.M., Ph.D. In addition to acknowledging the superior work by the trainees, Hoenerhoff said, "This award also reflects highly on the high standards of quality the NTP has achieved in terms of training and research."

"Ours is the only program of its kind in the U.S. and the world. Trainees learn rodent pathology, provide institute support, work on NTP projects, and prepare for board certification by the American College of Veterinary Pathologists (ACVP)," added Malarkey, who has been instrumental in establishing a formalized and successful NIEHS Toxicological Pathology Training Program. "There have been 13 pathology trainees in the program since 2003, with 11 becoming board-certified by the American College of Veterinary Pathologists (ACVP), and 4 simultaneously pursuing, or having received, a Ph.D. from NCSU [North Carolina State University]."

Well-deserved recognition

"Receiving first place in the Society of Toxicologic Pathology Young Investigator Awards is a very significant accomplishment for Dr. Bhusari," Hoenerhoff explained. "This award is one of many that he has been awarded during his time at NTP, and is really a testament to his dedication to toxicology and cancer research." Among Bhusari's earlier accomplishments was earning recognition as a Diplomate of the American Board of Toxicology (ABT), one of the profession's top certifications.

According to Malarkey, in addition to his work on NTP studies, Boyle also assists NIEHS intramural researchers in the design, implementation, and evaluation of animal studies. He is an ACVP board-certified veterinary pathologist, and currently pursuing certification by ABT, in addition to his Ph.D. research. ●

NTP postdoc takes top prize at NCSOT meeting

By Eddy Ball, reprinted from eFACTOR, October/November 2013



Unfortunately, Xu was unable to attend the meeting and make the oral presentation that was part of her first prize win. Her colleague, NTP biologist Erik Tokar, Ph.D., accepted the award plaque on her behalf. (Photo courtesy of Steve McCaw)

The main program, organized by chapter vice-president Christie Sayes, Ph.D., consisted of three talks on environmental health and ecological issues with specific relevance for the state of North Carolina. "We're branching a little away from the lab," DeWitt said of the program. "We went from the mountains with trees, to the coast with hurricanes, and finally to the piedmont and bees." ●

[Return to table of contents](#)

The [North Carolina Chapter of the Society of Toxicology \(NCSOT\)](#) held its annual fall meeting and awards ceremony for postdoctoral fellows Oct. 24 at NIEHS. The event featured presentations on the meeting theme, "From the Mountains to the Coast: Environmental Toxicology Research in North Carolina," by specialists from universities across the state.

Chaired by East Carolina University (ECU) toxicologist Jamie DeWitt, Ph.D., the meeting opened with presentation of the group's President's Award for Research Competition (PARC) to three area postdoctoral fellows, with first-place going Yuanyuan (Laura) Xu, Ph.D., a visiting fellow in the NTP Laboratories Inorganic Toxicology Group, headed by lead researcher Michael Waalkes, Ph.D.

In her winning abstract, Xu reported findings from a study on the contribution of inorganic arsenic exposure to the development of an important subset of breast cancers (see [text box](#)). Xu's award, her second PARC first place, included a monetary award and a place on the program.

Two postdoctoral fellows at the U.S. Environmental Protection Agency tied for second place. Samantha Snow, Ph.D., and Yong Ho Kim, Ph.D., also received cash prizes.



Tokar, right, was a coauthor on Xu's paper and a first-place PARC winner as a postdoctoral fellow in 2008 and 2009. (Photo courtesy of Steve McCaw)

NTP talk explores zebrafish as a vertebrate model in toxicity screening

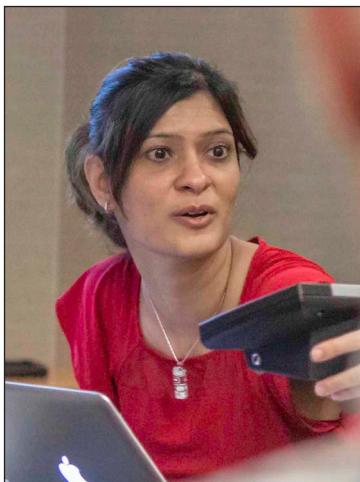
By Kristen Ryan, reprinted from eFACTOR, September 2013

Partnerships in zebrafish screening

NTP has several collaborations underway to examine the utility of zebrafish for screening and prioritizing chemicals, to ultimately serve as a model for *in vivo* hazard characterization:

- Robert Tanguay, Ph.D., at Oregon State University has tested over 3,000 compounds of interest to NTP, to complement the ongoing high-throughput screening efforts in the U.S. government's multiagency Tox21 research program. His research focuses on examining the effects of selected chemicals and chemical classes on zebrafish development and associated gene expression pathways (see related [story](#)).
- Christopher Weis, Ph.D., toxicology liaison in the NIEHS Office of the Director, and Stephanie Padilla, Ph.D., of the U.S. Environmental Protection Agency, are investigating the effects of flame retardants on zebrafish development, as well as behavior.

[Continued on next page](#)



Behl introduced Muriana, whose talk was broadcast from Spain. Behl also moderated the question-and-answer session. (Photo courtesy of Michael Garske)

Arantza Muriana, Ph.D., gave a presentation Aug. 19 on the utility of zebrafish for toxicity testing, speaking by telephone to a capacity audience of NTP and NIEHS scientists with interests in the advancement of predictive toxicology. Her talk, "Zebrafish as a Tool for Screening and Prioritization of Chemicals for Toxicity Testing," was hosted jointly by the NTP Toxicology Branch (TB) and Biomolecular Screening Branch (BSB).

Muriana is director of Research and Development Management for Biobide S.L., an international contract research organization offering preclinical testing for early drug development. Biobide's unique specialty is providing the opportunity to rapidly assess numerous and complex aspects of drug-induced or chemical-induced toxicity in zebrafish.

"The NTP has been interested in identifying new strategies for screening and prioritizing compounds for *in vivo* testing, especially with the increasing nominations of classes of compounds such as flame retardants, PAHs, and phenolic benzotriazoles (PBZT)," said NTP contract toxicologist Mamta Behl, Ph.D., presentation host. "The zebrafish is a powerful tool to screen compounds, especially for early development, since it is a vertebrate, has a high genetic homology with humans, and the assays can be automated to provide relatively high-throughput along with high-content analysis."

An emerging model for toxicology and drug development

As Muriana explained, the adult and developing zebrafish are well established as model organisms for studies of vertebrate development, gene expression, and behavior, with over 12,000 research papers published within the last 10 years. In particular, zebrafish embryos have many applications, including the assessment of chemicals for their potential acute toxicity and teratogenicity, as well as organ-specific toxicities, including cardiotoxicity, hepatotoxicity, and neurotoxicity. At Biobide, she said, these assays have been developed to perform with a high degree of sensitivity and specificity, and can also be conducted under GLP (Good Laboratory Practice) testing regulations.

During the seminar, Muriana highlighted the wide range of applications for toxicity testing in zebrafish, as well as Biobide's approach to refine and reduce the use of animals, while saving time and expense. At Biobide, a MultiTox Assay was developed to narrow down a large chemical set, by screening zebrafish through a particular sequence of assays, rather than performing one assay at a time.



BSB head Raymond Tice, Ph.D., described goals of the NTP predictive toxicology program. Seated beside him is Warren Casey, Ph.D., acting director of the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods, which has an explicit interest in refining and reducing the use of animals in testing. (Photo courtesy of Michael Garske)

Can the model work for NTP?

While zebrafish seem to be ideal for drug development, individuals such as NTP contract pathologist Deepa Rao, Ph.D., questioned how well this strategy would work for environmental chemicals, since very little is known about their toxicity profiles at the onset of testing. Muriana pointed out that Biobide can customize assays. In response to a question on throughput from NTP molecular toxicologist Scott Auerbach, Ph.D., she estimated that nearly 100 compounds could be tested across three assays within three months' time.

A lively discussion led to several interesting questions from the audience, including one by TB head Paul Foster, Ph.D., about whether or not these assays, using embryos at day five, can accurately capture necessary windows of development for the urogenital system. Foster wondered whether longer-term assays can be conducted, to evaluate the effects of chronic exposures.

Overall, the seminar strengthened the growing appreciation for the value of zebrafish in toxicity testing, and brought insight to the program for future alternative and complimentary testing strategies within NTP.

(Kristen Ryan, Ph.D., is an Intramural Research Training Award Fellow in the NTP Toxicology Branch.)



NIEHS holds high throughput toxicogenomics platforms workshop

By Kristen Ryan, reprinted from *eFACTOR*, October/November 2013



"Hopefully, by the end of this workshop, we will have identified the kinds of criteria we think are optimal for this gene prioritization process," Tice said. (Photo courtesy of Steve McCaw)

Leaders in the field of toxicogenomics met at NIEHS Sept. 16-17 to discuss the best methods for prioritizing approximately 1,000 genes for use in high-throughput toxicogenomics platforms.

The genes will be used for determining the effects of environmental toxins on cells or tissues from humans, rats, mice, zebrafish, and *Caenorhabditis elegans*. The High Throughput Transcriptomics Workshop — Gene Prioritization Criteria gave presenters an opportunity to summarize their respective gene sets, and discuss how these sets have been used to screen disease or toxic agent-related responses in cells from humans or rodents.

Advancing predictive toxicology with gene expression profiles

NIEHS Deputy Director Richard Woychik, Ph.D., welcomed the group. NTP Biomolecular Screening Branch Chief Raymond Tice, Ph.D., then addressed the workshop goals and how the gene list would be used to advance [Tox21](#), a collaboration between several federal agencies to research and test chemicals using high throughput screening methods.

"In our next phase of Tox21, we plan to focus on high content screens and high throughput gene expression platforms, which is where this workshop comes in," Tice said. "We want to identify a set of genes that could be applied to virtually any cell type, whether it is *in vitro* or *in vivo*, and would allow us to screen large numbers of cell samples in a short time at low cost."

Joel Dudley, Ph.D., of the Icahn School of Medicine at Mount Sinai, discussed how large scale data integration could be used to select genes of interest. Justin Lamb, Ph.D., of Genometry Inc., described the development of the Broad Institute L1000 assay, and performance of the platform for detecting toxic responses in cultured human cells.

NTP molecular toxicologist Scott Auerbach, Ph.D., gave his presentation remotely, and asked the audience, "How does one balance data-driven versus knowledge-driven gene selection?" He argued that it is important to include chemical genomics data when selecting genes — a practice he uses to weight his gene selections.

The remainder of the first day included talks from Richard Judson, Ph.D., of the U.S. Environmental Protection Agency (EPA); David Gerhold, Ph.D., of the National Center for Advancing Translational Sciences (NCATS); Henghong Li, M.D., Ph.D., of Georgetown University; and Lena Smirnova, Ph.D., of the Johns Hopkins Bloomberg School of Public Health.

Setting the stage for the project's future directions

Daniel Shaughnessy, Ph.D., a health scientist administrator in the NIEHS Division of Extramural Research and Training, outlined the workshop's focus for the second day, and set the stage for the morning's scheduled speakers. These included Ruili Huang, Ph.D., of NCATS; Avrum Spira, M.D., of the Boston University School of Medicine; Julia Gohlke, Ph.D., of the University of Alabama; Carolyn Mattingly, Ph.D., of North Carolina State University; and Christopher Willis, Ph.D., of Thomson Reuters.

The afternoon was reserved for discussion, which was led by NTP Deputy Division Director for Science Nigel Walker, Ph.D. Walker moderated several discussions ranging from the goals of the workshop, biological systems, technologies to be utilized, and the types of approaches best suited to select and prioritize genes.

One audience member wondered whether the central goal was to predict toxicity or disease. The majority of the group believed that predicting toxicity from a gene set was best suited for the proposed screening program. However, John Bucher, Ph.D., NTP associate director, said the aim was to determine overlap of chemically induced toxicity and disease pathways, to increase the probability of finding chemicals of interest to human health.

Tice concluded the workshop by providing a sequential set of future directions for the project, including the development of gene prioritization criteria based on responses to a request for information, publications, workshop presentations, and discussions. ●

(Kristen Ryan, Ph.D., is an Intramural Research Training Award Fellow in the NTP Toxicology Branch.)

NIEHS and NTP join colleagues at Teratology Society meeting

By Robin Mackar, reprinted from *eFACTOR*, August 2013



Shelby, at podium, and Howdeshell, second from right, of NTP, organized a panel of experts to discuss chemotherapeutic use and pregnancy outcomes. Howdeshell also made a presentation to the NTP Board of Scientific Counselors about the new NTP monograph that same week. (Photo courtesy of Gloria Jahnke)

The [Teratology Society](#) is a scientific group with a mission focused on preventing birth defects, including identification of environmental factors that affect maternal health and pregnancy outcomes. The important role this society plays in environmental health was very evident by the number of cutting-edge talks that NIEHS and NTP staff gave at its 53rd [annual meeting](#) June 22-26 in Tucson, Ariz.

Cutting-edge technologies

The theme of the annual meeting was Application of Cutting-Edge Technologies to Improve Assessment, Treatment, Prevention, and Communication Regarding Birth Defects. A special plenary lecture on "New experimental approaches for exploring the genetic/epigenetic landscape of environmental exposures" was presented by NIEHS

Deputy Director Rick Woychik, Ph.D. He was introduced by Teratology Society President Edward Carney, Ph.D., director of Predictive Toxicology at Dow Chemical Company. Woychik talked about efforts in his own laboratory to use diverse stem cell populations to understand the molecular mechanisms of toxicity.

Cancer and pregnancy symposium

Stemming from their work on the [NTP Monograph on Developmental Effects and Pregnancy Outcomes Associated with Cancer Chemotherapy Use During Pregnancy](#), Kembra Howdeshell, Ph.D., and Mike Shelby, Ph.D., of NTP's [Office of Health Assessment and Translation \(OHAT\)](#), organized and co-chaired a symposium on Cancer and Pregnancy: Considerations Regarding the Use of Chemotherapy. Howdeshell provided an overview of the finalized monograph, which was designed as a resource document for the pregnant patient with cancer and her medical team, as they consider treatment options. More than 100 people attended the session, which was co-sponsored by the [Organization of Teratology Information Specialists](#). The symposium also received funding from NIEHS.

"We are so pleased that we could accommodate this important symposium into our scientific program" said Carney. "NTP did its usual excellent homework and pulled together an impressive panel of speakers." Carney is familiar with NTP products, as he has served as an expert panel member for evaluations of the Center for the Evaluation of Risks to Human Reproduction (now OHAT) and as a member of the NTP Board of Scientific Counselors.

During the afternoon symposium, in addition to Howdeshell's presentation summarizing the NTP monograph, speakers included cancer and fertility specialists:

- Elyce Cardonick, M.D., an obstetrician at Cooper Health System, who focused on prenatal care for the pregnant cancer patient and the need for registries to document pregnancy outcomes.
- Jennifer Litton, M.D., an oncologist at the University of Texas MD Anderson Cancer Center, spoke about some of the latest methods used for detection and administration of systemic therapies for breast cancer during pregnancy.
- Laxmi Kondapalli, M.D., a reproductive endocrinologist and fertility expert at the University of Colorado Anschutz Medical Campus, updated attendees about the field of oncofertility, or the latest methods in fertility preservation in patients with cancer.

"The information the speakers provided will be of great value to any female cancer patient and her physicians, regarding decision-making for a current pregnancy or preservation of fertility for future pregnancies," Carney added. Howdeshell said she received some excellent ideas from the panelists and the participants about next steps for disseminating the new monograph.

Diabetes and pregnancy

Gloria Jahnke, D.V.M., of the NTP Office of the Report on Carcinogens, took the lead in heading another session. Chair of the Teratology Society's Public Affairs Committee for the past three years, Jahnke co-chaired a symposium on diabetes and pregnancy with Asher Ornoy, M.D., from the Israeli Teratology Information Service. The symposium was endorsed by the Society for Maternal-Fetal Medicine, and included a stellar panel that focused on addressing how to prevent or treat the increasing number of women with diabetes that become pregnant.

"One of the things I love about the Teratology Society meetings is the diverse group of disciplines represented by those who attend the meetings and make up its membership. It makes every symposium more interesting," Jahnke said.

Other NIEHS staff participating in the meeting included Suzanne Fenton, Ph.D., and Jason Stanko, Ph.D., from the NTP Laboratory [Reproductive and Endocrinology Group](#), and Thad Schug, Ph.D., from the Extramural Research and Training Division. ●

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

[Return to table of contents](#)

Talking toxicogenomics and global database

By Ernie Hood, reprinted from *eFACTOR*, August 2013



Alex Merrick, Ph.D., leader of the Molecular Toxicology and Informatics Group in the NTP Biomolecular Screening Branch, was one of more than 30 workshop participants, who brought a wide range of expertise to the meeting. Merrick joined NTP molecular toxicologist Scott Auerbach, Ph.D., who described the [DrugMatrix](#) database, a large toxicogenomics reference resource. (Photo courtesy of Steve McCaw)

The daunting challenges and astonishing opportunities presented by big data are currently attracting attention in many fields, including toxicogenomics, where technology is contributing to rapid expansion in the number and size of databases, most of which do not presently interact effectively. That premise spawned an international meeting at NIEHS June 26-27 titled Workshop on Identifying Opportunities for Global Integration of Toxicogenomics Databases.

More than 30 scientists from around the world, involved with toxicogenomics databases, attended the workshop, which was organized over the past year by Allen Dearry, Ph.D., and Rebecca Boyles, of the [NIEHS Office of Scientific Information Management](#); Jennifer Fostel, Ph.D., NTP scientific administrator of the [Chemical Effects in Biological Systems \(CEBS\)](#) database; and their colleagues Jos Kleinjans, Ph.D., and Diana Hendrickx, Ph.D., from Maastricht University in the Netherlands, who are involved with European Union (EU) toxicogenomics database initiatives.

An array of toxicogenomics databases

The first day of the workshop was devoted to presentations about the many toxicogenomics databases around the world, all of which are somewhat different in their contents and approaches. "It was good for everybody to see the scope of all of the various toxicogenomic databases, as people got some familiarity with the universe of databases that are out there," said Dearry. "And then the next step is to try to see what we can do to start to enable cross talk between them."

During the second day of the gathering, the group engaged in discussions designed to yield concrete action plans. Participants identified three types of problems in need of attention — database communication, such as metadata consensus and definition of standards; sustainability, such as funding continuity and data preservation; and the need for education in the field to ensure an adequate and trained future workforce.

Continued on next page

First things first

Attendees quickly recognized that, in order to effectively and efficiently tackle such a complex undertaking, solid information about the wants, needs, and goals involved will be necessary prior to moving forward. Boyles posed provocative initial questions to the group about what they expect to gain by interoperability in this field. “This is a lot of time, effort, and, therefore, money, so you’d better be sure that what we’re pursuing is going to add some value to the field.”

With those challenges in mind, step one of the group’s action plan involves research. “The action plan really has some concrete steps in terms of developing our own inventory of what the toxicogenomics databases are, going out and searching for some use cases about toxicogenomics research and how these databases can be useful in that, and then using all of that information to develop a white paper to try to explain what this integration can bring about and why it would be useful to the larger research community,” Boyles explained.

The goal is to have that research accomplished by mid-September, in time for the Research Data Alliance (RDA) [Second Plenary Meeting](#), Building Global Partnerships, Sept. 16-18 at the National Academy of Sciences in Washington, D.C. The RDA is a consortium arrangement among organizations in the U.S., EU, and Australia that aims to accelerate and facilitate research data sharing and exchange. Much of its work is accomplished by its working groups and interest groups, so the intent would be to propose establishment of an RDA special interest group to provide a formal mechanism and framework for enhancing interoperability of toxicogenomics databases. ●

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

[Return to table of contents](#)

ICCVAM

By Robin Mackar, reprinted from *eFACTOR*, October/November 2013



Casey discussed the need to take advantage of ongoing activities in the U.S. and internationally that are working on the development of alternative tests. (Photo courtesy of Steve McCaw)

Over the past nine months, representatives from 15 federal agencies have been working together to reinvent how they do business. Members of the Interagency Coordinating Committee on the Validation of Alternative Methods ([ICCVAM](#)) presented Sept. 24, a new vision and direction to their external advisors, the Scientific Advisory Committee on Alternative Toxicological Methods ([SACATM](#)).

“We praise Dr. Birnbaum for stepping up to the plate and changing the way the committee will operate,” said SACATM member Ricardo Ochoa, D.V.M., Ph.D., president of Pre-Clinical Safety Inc. Ochoa was referring to an [editorial](#) written earlier this year by NIEHS and NTP Director Linda Birnbaum, Ph.D., in which she called for a reinvention of ICCVAM.

In her editorial and during opening remarks at the public meeting, Birnbaum called for the ICCVAM agencies to take a more active role in setting the priorities of the committee.

“Rather than the NIEHS directing the activities of ICCVAM..., the interagency agenda will now be driven by the partner regulatory agencies — the agencies that will ultimately implement the ICCVAM-recommended methods,” said Birnbaum.

ICCVAM was established by [Congress in 2000](#), to reduce, replace, or refine the use of animals in toxicity testing.

ICCVAM priority areas

Anna Lowit, Ph.D., from the U.S. Environmental Protection Agency (EPA), interim co-chair of ICCVAM, presented an overview of the committee’s draft [“A New Vision and Direction for ICCVAM,”](#) which includes setting immediate priorities, improving communications with stakeholders and the public, and exploring new paradigms to validate and use alternative toxicological methods.

Continued on next page



Lowit identified several projects that ICCVAM believes can be successful in the short term. These areas include biologics, or non-animal methods, for testing vaccines that protect pets and livestock against the disease leptospirosis; acute oral testing to identify substances that could be poisonous when ingested or absorbed through the skin; and skin sensitization, or testing, to identify substances that could cause allergic contact dermatitis.

SACATM members agreed with the priority areas, although some members, like Daniel Wilson Ph.D., from Dow Chemical Company, told the group to not forgo some of the other areas they were pursuing, such as skin and eye irritation methods.

Separation of powers

NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) acting director Warren Casey, Ph.D., led the discussion on what role NICEATM will play in ICCVAM with a dramatic, but encouraging, analogy. Referring to the spacecraft Voyager, he made the point that working on alternative test methods is like the challenge put forth in the 1960s to put a man on the moon.

“Replacing animals is our challenge, but it is possible,” Casey said. “We just need to work together and take advantage of the advances being made in science and technology.”

Casey noted that NICEATM will continue to provide administrative and scientific support for ICCVAM, but there will be more of a separation of powers, to ensure ICCVAM activities are driven by agency needs and approved by consensus.

To this end, Casey noted the appointment of Raymond Tice, Ph.D., chief of the NIEHS [Biomolecular Screening Branch](#), to serve as the Institute’s principal ICCVAM representative. Tice is also the NIEHS and NTP lead for Tox21, a multiagency effort that uses high throughput and other cutting-edge technologies to assess the safety of chemicals. Both ICCVAM and NICEATM are expanding their efforts to work more closely with Tox21, which represents a new paradigm shift for [toxicity testing](#).

Agency updates



Birnbaum with outgoing SACATM chair Steven Niemi, D.V.M. (Photo courtesy of Steve McCaw)

Afternoon speakers included Joanna Matheson, Ph.D., of the U.S. Consumer Product Safety Commission, discussing adverse outcome pathways (AOPs). Tice provided an overview of Tox21 activities, and Richard McFarland, M.D., Ph.D., from the U.S. Food and Drug Administration (FDA), and Geetha Srinivas, D.V.M., Ph.D., of the U.S. Department of Agriculture, reported on international vaccine workshops.

Casey concluded by showing the declining number of test method submissions going to one of ICCVAM’s international partners, the European Centre for the Validation of Alternative Methods (ECVAM). Unlike its U.S. counterpart, ECVAM was specifically set up with resources, staff, and labs to scientifically validate alternative methods that research laboratories have developed.

“There are not many new methods coming through the pipeline,” Casey added. “We have to turn to science to do something different.” ●

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



Tice, far right, joined Christine Kelley, Ph.D., center, the NIH ICCVAM representative, and Pertti (Bert) Hakkinen, Ph.D., from the National Library of Medicine, at the SACATM meeting. Tice will now serve as the NIEHS principal representative to ICCVAM. (Photo courtesy of Steve McCaw)



The interim co-chairs for ICCVAM, Anna Lowit, Ph.D., from EPA, and Abigail Jacobs, Ph.D., from FDA, represented the 15 member agencies that make up ICCVAM, at the meeting. (Photo courtesy of Steve McCaw)



Subscribe to the NTP Listserv

To subscribe to the listserv and receive the NTP Update as well as other NTP news and announcements electronically, register online at <http://ntp.niehs.nih.gov> or send e-mail to ntpmail-request@list.niehs.nih.gov with the word "subscribe" as the body of the message or contact the NTP Office of Liaison, Policy and Review. Additional information about the NTP along with announcements of meetings, publications, study results and its centers is available on the Internet at <http://ntp.niehs.nih.gov>.

The NTP website offers electronic files of the Report on Carcinogens and the library of NTP Technical Reports and NTP Toxicity Reports. The PDF files of these reports are available free-of-charge through the NTP website at <http://ntp.niehs.nih.gov> (see Resources).

Contact Information: NTP Office of Liaison, Policy and Review, NIEHS, P.O. Box 12233, MD K2-03, Research Triangle Park, NC 27709; T: (919) 541-0530; FAX: (919) 541-0295; CDM@niehs.nih.gov

NTP Study Reports and Publications Available at: <http://ntp.niehs.nih.gov/go/reports>

[Return to table of contents](#)