



The 2016 Global Summit on Regulatory Science (GSR16) with the theme of “Nanotechnology Standards and Applications” was held at the National Institutes of Health (NIH) Campus in Bethesda, MD on September 7-9 and was hosted by FDA, the Global Coalition for Regulatory Science Research, and the Arkansas Research Alliance.

Panel discussions and speaker presentations, including FDA Commissioner Dr. Robert M. Califf, explored the most immediate research needs in nanotechnology science, measurement methods, and standards relevant to regulatory applications. The international conference provided a forum for scientists from government, industry, and academia from 19 countries to facilitate coordination of the development of these emerging technologies and standards to improve regulatory processes.

For more information, contact William Slikker, Jr., Ph.D., Director, FDA/NCTR.



NCTR Summer Student Research Program

NCTR concluded its 2016 Summer Student Research Program with oral presentations by the young investigators describing their summer research projects and results. This year’s program hosted 30 students representing U.S. colleges and universities from 18 different states, and was funded by FDA’s Office of Minority Health, Society of Toxicology’s Education

Committee, and NCTR. The 10-week program paired both undergraduate and graduate students one-on-one with NCTR scientists to provide hands-on research experience in the practice of regulatory science.

The Summer Student Research Program is designed to introduce students to the possibilities of careers in toxicology and regulatory sciences in the public service sector. For additional information, contact Laura Schnackenberg, Ph.D., Division of Systems Biology, FDA/NCTR.

Central Arkansas Undergraduate Research Symposium

Twenty-two undergraduates from NCTR's Summer Student Research Program participated in the 5th Annual Central Arkansas Undergraduate Research Symposium held July 20, 2016, at the University of Arkansas for Medical Sciences. The students presented a total of 19 poster presentations and three oral presentations of their 10-week summer research projects.

Awards were given for the top three posters and top three oral presentations. One NCTR student received 3rd place overall in the poster session (91 posters total) and another received 1st place overall in the oral presentations (12 oral presentations total).

Participation in this annual symposium allows NCTR to partner with other summer undergraduate research programs throughout Arkansas to support training and professional development for the next generation of scientists.



Arkansas Research Alliance

Selects Two New Fellows from NCTR

Weida Tong, Ph.D., Director of NCTR's Division of Bioinformatics and Biostatistics and Paul Howard, Ph.D., Director of NCTR's Office of Scientific Coordination were announced as Arkansas Research Alliance (ARA) Fellows on September 8, 2016 at the Arkansas State Capitol. According to the ARA Website, the Fellows program was created to advance the mission of ARA by supporting world-class scholars whose work helps strengthen the competitiveness of the state through university-based research. Since the ARA was founded in 2008, ten fellows have been chosen.

Tong's work at the National Center for Toxicological Research focuses on developing methods to support FDA research and regulations. Howard's work is concentrated on food contaminants, cosmetic ingredients, tattoo ink, and nanotechnology-based materials.

Operating as a public-private partnership, ARA invests in research that stimulates innovation, encourages collaboration, and strengthens economic opportunity in areas in which Arkansas possesses core competency. [Learn more about the Arkansas Research Alliance.](#)

4th Annual FDA Scientific Computing Days

The 4th Annual FDA Scientific Computing Days event, hosted by the FDA Scientific Computing Board, was held September 27-28, 2016, at the FDA White Oak campus. This year's theme was "Innovating in Regulatory Science Through Scientific Computing to Promote Public Health." In addition to keynote speakers from industry, academia, and government there were poster sessions and interactive breakout sessions — open to FDA only — designed to discuss the successes, challenges, and opportunities for scientific computing.

Annie Lumen, Ph.D., from NCTR's Division of Biochemical Toxicology co- led one of these breakout sessions on the topic of chemical-based models.

The meeting, while focused on FDA, was open to the public with the goals to:

- Raise awareness about FDA activities in scientific computing.
- Help foster collaboration and improve networking.
- Promote the use of scientific computing for regulatory decision making.
- Learn from one another about different approaches to scientific computing.



FDA Commissioner Visits NCTR

Photo by Benjamin Krain

AR Governor Asa Hutchison (seated left) and Robert M. Califf, MD., Commissioner of the Food and Drug Administration (seated right), sign a memorandum of understanding extending a federal-state partnership regarding the FDA's National Center for Toxicological Research.

On August 31, 2016, NCTR hosted FDA Commissioner, Dr. Robert M. Califf. During his visit, Dr. Califf, NCTR Director Dr. William Slikker, Jr., and Arkansas Governor Asa Hutchinson met at the Arkansas State Capitol to renew the Memorandum of Understanding (MOU) between FDA, NCTR, and the State of Arkansas. The MOU, the first of its kind, sets general guidelines for FDA and Arkansas to discuss topics of mutual benefit.

Following the MOU signing, Dr. Califf toured NCTR and the Office of Regulatory Affairs' Arkansas Regional Laboratory on the FDA Jefferson Laboratories Campus and visited with staff. Dr. Califf was accompanied by representative product reviewers and administrators from FDA's Center for Drug Evaluation and Research, Center for Devices and Radiological Health, and Center for Biologics Evaluation and Research. Discussions centered on:

- Identifying mechanisms for improving communication and collaboration between the Centers
- Identifying critical questions of mutual concern to foster scientific research
- The potential to cooperate on continued education of the respective staffs.

For more information about the MOU, contact William Slikker, Jr., Ph.D., Director, FDA/NCTR.

[Watch the MOU signing at the Arkansas State Capitol.](#)



Bacterial Populations Associated with Smokeless Tobacco Products

Scientists from FDA's NCTR and Center for Tobacco Products completed a microbiological characterization study of 15 common smokeless tobacco products (STPs) and identified several bacterial species capable of reducing nitrates to nitrites, which could lead to the formation of carcinogenic tobacco-specific nitrosamines. The results of this study provide a microbiological baseline for some STPs and provide information that may inform regulatory activities related to STPs. A manuscript detailing this study is available online at [Applied and Environmental Microbiology](#).

For additional information, contact Steve Foley, Ph.D., Division of Microbiology, FDA/NCTR.



Dietary Influences on Toxicology Study Outcomes

NCTR's dietary studies suggest that subclinical micronutrient deficiencies could impact the results of toxicology studies. Additionally, the role of subclinical micronutrient deficiencies in reproductive deficits in animals and humans may warrant attention. A range of endpoints typically evaluated in general and reproductive toxicity studies were evaluated in mice that were fed a series of natural- and purified-ingredient diets with variable levels of soy protein and soy isoflavones. Significant differences in endpoints such as body weight, insulin, glucose blood levels, and time to first estrus were observed among diet groups. A deficit in sperm production in one diet group appeared to be related to an unanticipated micronutrient deficiency, and this

effect on spermatogenesis was observed in the absence of other significant clinical signs.

Diet selection for toxicology testing should be considered, complete formulations should be reported, and evaluations for the level of nutrients should be tested to enhance the interpretability of study results. A manuscript detailing the study is available online at [Food and Chemical Toxicology](#).

For additional information, contact Barry Delclos, Ph.D., Division of Biochemical Toxicology, FDA/NCTR.



Studies on Postoperative Cognitive Dysfunction (POCD): Isoflurane Anesthesia Does Not Impair Aspects of Cognitive Function in Aged Rats

Scientists from NCTR and the University of Toronto have shown that aged rats anesthetized with 1.3% isoflurane demonstrated no residual effect on aspects of impulsivity, counting, learning, and motivation. Compared to controls that received medical grade air, 23-month-old rats exposed to 1.3% isoflurane for a single two-hour period showed no impairment in operant performance testing. The testing included fixed consecutive number, incremental repeated acquisition, and progressive ratio tasks. Additionally, rats exposed to repeat exposures up to six hours in duration also showed no deficits in these operant performance tasks.

POCD is a post-surgery complication in elderly patients characterized by deficits in information processing, memory, and executive function. These results indicate that isoflurane effects may be selective to spatial memory tasks rather than to other cognitive domains. A manuscript detailing this study is available online at [NeuroToxicology](#).

For additional information, contact Merle Paule, Ph.D., Director, Division of Neurotoxicology, FDA/NCTR.

Modeling Compound Binding to the Estrogen Receptor

NCTR scientists have developed a unique modeling approach to improve the ability to predict estrogen receptor binding activity of unknown chemicals. This model is known as three-dimensional spectrometric data activity relationship (3D-SDAR). Compared to alternative modeling techniques, 3D-SAR displayed very little reduction in sensitivity (ability to identify true positives) and specificity (ability to identify true negatives) performance between the training set and an external prediction set. The strength of the model is inherent in its ability to identify structural features essential for a compound to act as an estrogen.

There is an ongoing concern that drugs and/or environmental contaminants may have developmental and/or reproductive effects by interfering with hormone function. Predictive models could serve to identify and prioritize the compounds of highest concern. A manuscript describing this study is available online at [Environmental Toxicology and Chemistry](#).

For additional information, contact Richard Beger, Ph.D., Director of Biomarkers and Alternative Models Branch, Division of Systems Biology, FDA/NCTR.



Identification of a Potential Plasma Biomarker of Liver Injury

Scientists from NCTR and the National Institute on Alcohol and Abuse and Alcoholism identified an increase in the protein-expression levels of heme oxygenase 1 (HMOX1) in plasma from rats treated with acetaminophen (APAP). The proteomic study quantitatively analyzed liver tissues collected from rats at 6 hours and 24 hours after treatment with low (100 mg/kg) and high (1250 mg/kg) doses of APAP. The study identified 31 proteins correlated to liver damage. Of these, an increase in HMOX1 plasma levels was also associated with liver injury in APAP-treated rats and in mice, as part of a cross-species verification study.

These data suggest the potential of HMOX1 as a plasma biomarker of liver injury, although further investigation with larger studies to address clinical

specificity and sensitivity are required. A manuscript describing the study is now available online at [Proteomics Clinical Applications](#).

For more information, contact Li-Rong Yu, Ph.D., Division of Systems Biology, FDA/NCTR.



Species Identification of Food-Contaminating Beetles

Scientists from FDA's NCTR and Office of Regulatory Affairs/Arkansas Regional Laboratories developed a pattern-recognition algorithm to identify food-contaminating beetles at the species level. The identification was based on microscopic images of fragments of elytra (hardened forewings), with an overall accuracy of 80%. In this preliminary project, elytra from 15 common beetle species found in storage products were imaged with a microscope, and distinctive characteristics were quantified and used as inputs to artificial neural networks for species classification.

Species identification of beetle fragments can be an indicator of insanitation or food safety hazards and is a crucial step in food-contamination inspections, which are currently conducted by human analysis. This study demonstrates the potential for modern pattern-recognition systems to provide a faster and more cost-effective approach to food inspection. A manuscript detailing the study is available online at [PLoS ONE](#).

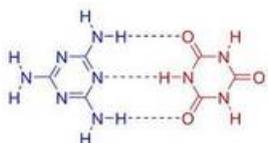
For additional information, contact Zhihua Xu, Ph.D., Division of Bioinformatics and Biostatistics, FDA/NCTR.

Model to Predict Severity of Drug-Induced Liver Injury (DILI) in Humans

Scientists from NCTR and Hannover Medical School (Germany) have developed an algorithm to quantitatively estimate the severity of drug-induced liver injury associated with an oral medication. This predictive model — DILIScore — improves upon a previous model, the Rule-of-Two (RO2) that only assesses DILI in a binary fashion (yes/no). DILIScore includes reactive metabolite formation in addition to the daily dose and logP originally considered by the RO2 model. DILIScore has the ability to

distinguish between different DILI severity within drug pairs that are defined as structurally similar and that have a similar mode-of-action. A manuscript describing the study is available online at [Hepatology](#).

For additional information, please contact Weida Tong, Ph.D., Division of Bioinformatics and Biostatistics, FDA/NCTR.



Potential Serum microRNA (miRNA) Biomarkers of Kidney Damage Identified

NCTR scientists demonstrated dose-dependent changes in the levels of serum miRNAs in male and female rats that were fed melamine and cyanuric acid (MEL&CYA) over a 28-day period. Using quantitative real-time PCR, two serum miRNAs – miR-128-3p and miR-210-3p – were shown to have decreased in male rats treated with 180 ppm MEL&CYA. This dose of 180 ppm produced kidney damage without altering the levels of blood urea nitrogen or serum creatinine, current biomarkers of kidney damage.

These experiments suggest that select serum miRNAs reflect the nephrotoxicity induced by co-exposure to MEL&CYA and have potential as sensitive biomarkers of kidney damage. This study was conducted at NCTR through funding from the Interagency Agreement between FDA/NCTR and the National Institute of Environmental Health Sciences/National Toxicology Program. A manuscript describing the study is available online at [Food and Chemical Toxicology](#).

For more information, contact Luísa Camacho, Ph.D., Division of Biochemical Toxicology, FDA/NCTR.

Silver Nanoparticle Effects on Intestinal Permeability

NCTR scientists demonstrated a dose-dependent increase in intestinal permeability in an *in vitro* model of human-colonic epithelial cells treated with 10 nanometer (nm) silver nanoparticles (AgNPs). However, no effects were observed when treated with 20, 75, or 110 nm AgNPs. At the 10 nm size, AgNPs were detected within cells and silver was able to pass through the epithelial-cell monolayer, thus indicating both penetration of AgNPs into

cells and passage of AgNPs or derivatives through the epithelial barrier. Additionally, exposure to 10 nm AgNPs resulted in the upregulation of genes involved in maintaining the epithelial barrier, possibly indicating an attempt to compensate for increased permeability.

The results of this study suggest that gastrointestinal exposure to small-size AgNPs could potentially compromise the integrity of the intestinal epithelium and disrupt barrier function which could have health consequences for the gastrointestinal tract. This study is currently available online at [Journal of Nanobiotechnology](#).

For additional information, contact Sangeeta Khare, Ph.D., Division of Microbiology, FDA/NCTR.



2016 International Conference on Neuroprotective Agents

NCTR scientists presented their recent research results at the 13th International Conference on Neuroprotective Agents (ICNA) held September 18-21, 2016, in Bilbao, Spain. The topics of presentations included:

- Relationship between anesthetic-induced toxicity and NMDA receptor-mediated calcium influx in developing neurons
- Acetyl-L-carnitine prevents long-lasting cognitive deficits in nonhuman primates after neonatal general anesthesia induced by nitrous oxide/isoflurane
- Anesthetic-induced developmental neurotoxicity in animal models that suggest potential clinical neuroprotective approaches
- Down-regulation of 14-3-3 proteins in kainic acid-induced neurotoxicity model
- A working module of the neurovascular unit in the sexually dimorphic nucleus of the preoptic area
- Traumatic brain injury induces blood-brain barrier dysfunction *in vitro*.

The goal of the ICNA is to provide a forum for clinical- and basic-science researchers from many countries and disciplines to address approaches to

neuroprotection and discuss therapeutic agents and medical devices that may have neuroprotective potential.

For more information, contact Tucker Patterson, Ph.D., Associate Director, Office of Regulatory Compliance and Risk Management, FDA/NCTR.



[View NCTR's Recent Scientific Publications](#)

For more information about NCTR contact Dr. William Slikker, Jr., NCTR Director at William.Slikker@fda.hhs.gov or (870) 543-7517.

Links within documents:

Learn more about the Arkansas Research Alliance -

http://www.aralliance.org/?source=govdelivery&utm_medium=email&utm_source=govdelivery

Watch the MOU signing at the Arkansas State Capitol -

https://www.youtube.com/watch?source=govdelivery&utm_medium=email&utm_source=govdelivery&v=8B5J_GIApDw

Bacterial Populations Associated with Smokeless Tobacco Products

"Applied and Environmental Microbiology" –

http://aem.asm.org/content/early/2016/08/08/AEM.01612-16?source=govdelivery&utm_medium=email&utm_source=govdelivery

Dietary Influences on Toxicology Study Outcomes "Food and Chemical Toxicology"–

<http://www.sciencedirect.com/science/article/pii/S0278691516301594>

Studies on Postoperative Cognitive Dysfunction (POCD): Isoflurane Anesthesia Does Not Impair Aspects of Cognitive Function in Aged Rats "NeuroToxicology" -

http://www.sciencedirect.com/science/article/pii/S0161813X16301395?source=govdelivery&utm_medium=email&utm_source=govdelivery

Modeling Compound Binding to the Estrogen Receptor "Environmental Toxicology and Chemistry" –

http://dx.doi.org/10.1002/etc.3578?source=govdelivery&utm_medium=email&utm_source=govdelivery

Identification of a Potential Plasma Biomarker of Liver Injury "Proteomics Clinical Applications" -

http://dx.doi.org/10.1002/prca.201600123?source=govdelivery&utm_medium=email&utm_source=govdelivery

Species Identification of Food-Contaminating Beetles "PLoS ONE" -

http://dx.doi.org/10.1371/journal.pone.0157940?source=govdelivery&utm_medium=email&utm_source=govdelivery

Model to Predict Severity of Drug-Induced Liver Injury (DILI) in Humans "Hepatology" -

http://dx.doi.org/10.1002/hep.28678?source=govdelivery&utm_medium=email&utm_source=govdelivery

Potential Serum microRNA (miRNA) Biomarkers of Kidney Damage Identified "Food and Chemical Toxicology" -

http://www.sciencedirect.com/science/article/pii/S0278691516303283?source=govdelivery&utm_medium=email&utm_source=govdelivery

Silver Nanoparticle Effects on Intestinal Permeability "Journal of Nanobiotechnology" -

http://dx.doi.org/10.1186/s12951-016-0214-9?source=govdelivery&utm_medium=email&utm_source=govdelivery

NCTR Recent Scientific Publications -

http://www.accessdata.fda.gov/scripts/publications/more.cfm?center=NCTR¢er_name=Toxicological&source=govdelivery&utm_medium=email&utm_source=govdelivery