FDA / NCTR Quarter Page

Research Highlights, Activities, and Publications (Vol. 15, Issue 1: October-March 2016)

Developments for Early Detection of Doxorubicin Cardiotoxicity

Collaborating scientists from NCTR, the National Cancer Institute, Korea University, and UltraPath Imaging have identified a panel of 61 energy metabolism and apoptosis genes from doxorubicin (DOX)-treated mice that are differentially expressed in heart mitochondria prior to and after evidence of drug-induced cardiac injury. This suggests the genes may be used as potential early indicators of cardiotoxicity. Some of the 61 genes were differentially expressed at all cumulative dose levels (6-24 mg/kg DOX) administered at 3 mg/kg/week. Plasma levels of cardiac troponin T (cTnT) increased at 18 and 24 mg/kg cumulative DOX dosages and frank cardiac injury was detected by pathology assessment at the high, 24 mg/kg dose. The cardioprotectant drug, dexrazoxane, significantly reduced gene expression alteration and cTnT plasma levels, and eliminated cardiac pathology at the high dose.

DOX is an effective chemotherapeutic that is limited by an average lifetime-dose toxicity. Early biomarkers of drug-induced cardiotoxicity could enable an individualized approach to chemotherapeutic treatment. Information about the study is available online at *Toxicology and Applied Pharmacology.*

For additional information, please contact Varsha Desai, Ph.D., Division of Systems Biology, NCTR.

Early Doxorubicin-Induced Metabolomic Changes in Heart and Plasma

NCTR scientists measured significant early alterations in the levels of multiple metabolites in blood and heart tissue from mice treated with doxorubicin (DOX). The following were significantly altered in plasma from mice that received a cumulative DOX dose of 6 mg/kg (administered at 3 mg/kg/week) before cardiac troponin and histopathological cardiac injury was detected at the 18 and 24 mg/kg cumulative doses, respectively: 16 amino acids, 2 biogenic amines, 16 cylcarnitines, lactate, succinate.

Additionally, 18 amino acids and 4 biogenic amines were altered in heart tissue at the same cumulative dose level. These early metabolic changes observed in plasma during the initial stages of DOX-induced cardiac injury could be candidates for early biomarkers of cardiotoxicity. DOX is an effective chemotherapeutic that is limited by a lifetime dose due to cardiotoxicity; and early biomarkers of cardiotoxicity could have clinical applications for individualized treatment. A manuscript describing the study is now available at Journal of Applied Toxicology.

For additional information, please contact Laura Schnackenberg, Ph.D., Biomarkers and Alternative Models Branch, Division of Systems Biology, NCTR.

The 2015 Global Summit on Regulatory Science (GSRS15) with the theme of “Regulatory Bioinformatics” was hosted by FDA and the European Food

Safety Authority (EFSA) in Parma, Italy, on October 12-13, 2015. Roundtable discussions and speaker presentations, including Acting FDA Commissioner Dr. Stephen Ostroff, explored the applications and regulatory aspects of bioinformatics technologies. The international conference provided an opportunity for scientists from government, industry, and academia from 25 countries to discuss the potential for development and application of emerging technologies that could improve regulatory processes.

Prior to the summit, the Executive Committee of the Global Coalition for Regulatory Science Research (GCRSR) was briefed on progress from the Bioinformatics, Nanotoxicology, and Emerging Technologies Working Groups. Future GCRSR goals for training and collaborative research and options for the GSRS16 were also discussed.

For additional information, please contact William Slikker, Jr., Ph.D., Director, FDA/NCTR**.**

2016 Global Summit for Regulatory Science

Dates: September 7-9, 2016

THEME: Nanotechnology Standards and Applications

LOCATION: Natcher Auditorium, National Institutes of Health, 9000 Rockville Pike, Bethesda, Maryland USA

Nanotechnology for Healthcare Conference

The NCTR-ORA Nanotechnology Core Facility co-organized the sixth Nanotechnology for Healthcare Conference, held December 2-4, 2015, in partnership with the University of Arkansas for Medical Sciences, University of Arkansas at Fayetteville, University of Arkansas at Little Rock, and the Winthrop Rockefeller Institute. The keynote address to the Conference was delivered by the 1996 Nobel Laureate in Chemistry, Sir Harold Kroto on the topic of C60 fullerenes or “Buckyballs.” The keynote address was followed by research presentations delivered by national and international scientists on standardization of materials supporting regulatory review and novel nanotechnology-based disease diagnostics and therapeutics.

For additional information, please contact Anil Patri, NCTR Director, NCTR-ORA Nanotechnology Core Facility or visit the conference website .

NCTR Director Delivers Keynote Address to Chinese Society of Toxicology

NCTR Director, William Slikker, Jr., provided the invited keynote address to the Chinese Society of Toxicology in Wuhan, China on October 26, 2015. Over 1,200 attendees were present to hear his presentation entitled “World Impact of 3D Cell Models and Microphysiological Systems on Drug and Chemical Safety Assessment.” He also visited with the leadership of the National Institute of Food and Drug Control, Chinese FDA and visited their soon-to-open facility on the outskirts of Beijing.

NCTR Scientist Recognized with "2016 Transational Impact Award"

The Society of Toxicology (SOT) presented Dr. Richard Beger, Division of Systems Biology, with the 2016 Translational Impact Award on March 13, 2016. The award citation outlined Dr. Beger's leadership "using computational modeling, metabolomics, and proteomics to develop translational approaches to improve drug safety, disease detection/management, and human health." Dr. Beger's award address was titled, "Translational Non-Invasive Biomarkers of Acetaminophen-Induced Liver Injury."

Dr. Beger is the co-inventor of a unique Quantitative Spectrometric Data Activity Relationship, a modeling technique that has been used to predict efficacy and toxicity. A recent model used by FDA's Center for Drug Evaluation and Research predicts the adverse outcome of drug-induced phospholipidosis. Dr. Beger's and his colleagues' work with metabolomics studies has characterized biomarkers in preclinical studies that have carried into the clinic, improved drug safety and individualized patient care. Results of kidney toxicity studies in animals and in the clinic can be used to evaluate kidney damage in children undergoing cardiopulmonary bypass surgery. Similarly, biofluid-accessible biomarkers of hepatotoxicity are used to assess damage in children undergoing therapeutic treatment or with overdose of acetaminophen.

Learn more online at Society of Toxicology under "Translational Impact Award." For additional information contact William Slikker, Jr., Ph.D., Director, NCTR or Richard Beger, Ph.D., Director, Biomarkers and Alternative Models Branch, Division of Systems Biology, NCTR.

Human Infant Intestinal Microbiota as a Reservoir of Antimicrobial Resistance

Studies of the microbiota of mothers and their infants by collaborators at NCTR, the Norwegian University of Life Sciences, and the University of Reading in the United Kingdom, demonstrated that intestinal microbiota could serve as a reservoir of antimicrobial-resistance genes. This suggests the careful selection of antibiotics is an important consideration for the treatment of infections. High-throughput sequence analyses indicated a 15% prevalence of integrons in the study population of 147 mothers and their infants, which were typically associated with antimicrobial-resistance genes. These integrons were likely carried on potentially transmissible plasmids and were more stable than the overall bacterial populations. This may explain why the integrons persisted, even though there were changes in the bacterial population structure.

For additional information, please contact Steven Foley, Ph.D., Division of Microbiology, NCTR or refer to *Nature's Scientific Reports*.

Effects of Silver Nanoparticles on Accumulation, Distribution, and Toxicity

NCTR scientists conducted a 13-week study in rats to determine the differential accumulation, distribution, and potential toxicity of silver nanoparticles (AgNPs) administered daily by mouth. Significant AgNP accumulations in tissues and organs were observed to be both dose- and size-dependent. Additionally, sex differences were noted with female rats having significantly higher accumulations than males in the kidney, liver, jejunum, and colon. No significant changes in body weight or food/water intake and no treatment-related histopathological results were identified. AgNPs are widely used in consumer products and their use in the food industry has raised public concern related to safety, toxicity, and health

risks. These studies were conducted at NCTR under the auspices and funding of the Interagency Agreement between FDA's NCTR and the National Institute of Environmental Health Sciences' National Toxicology Program. A manuscript describing the study is available online at *Toxicological Sciences*.

For additional information, please contact Mary Boudreau, Ph.D., Division of Biochemical Toxicology, NCTR.

Dr. Merle Paule, Director of the Division of Neurotoxicology, gave a presentation at the 5th PANDA (Pediatric Anesthesia and NeuroDevelopment Assessment) Symposium held in New York, NY, on April 16-17, 2016. The presentation focused on NCTR's nonhuman primate studies on the long-lasting cognitive deficits associated with neonatal general anesthesia. The symposium, sponsored in part by the SmartTots public-private partnership between the FDA and the International Anesthesia Research Society (IARS), provides a forum for presentation and discussion of clinical and preclinical anesthesia studies being conducted at multiple U.S. institutions.

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

Novel Application of Text Mining Methods to Identify Transcriptional Targets

Scientists from FDA's NCTR and NIH's National Center for Advancing Translational Sciences (NCATS) applied a text mining method (author topic modeling) to integrate two different types of assay data (small molecule bioassays from Tox21 and *in vitro* human gene expression profiles from the Japanese Toxicogenomics Project) to discover transcriptional targets regulated by nuclear receptors. This novel application of text mining methods resulted in effective identification of associated/affected nuclear receptors and their target genes and provided biologically meaningful hypotheses embedded in their relationships. The study demonstrated that text mining methodologies can be an effective systems biology approach for integration of diverse sources of data from different technologies for an enhanced understanding of underlying mechanisms of disease and toxicity. A manuscript detailing the study is available online at *Toxicological Sciences*.

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

Visitors to NCTR

Thomas W. Jones, Ph.D., Chief Scientific Officer, Toxicology and Pathology, Eli Lilly and Company

Seminar: "Is It Safe? Understanding the Performance of Nonclinical Safety Assessment Models in Predicting Human Outcomes"

Dr. Jones' career at Eli Lilly has included a variety of technical and administrative roles. Currently, as Chief Scientific Officer for the Toxicology and Pathology organization, Dr. Jones has administrative responsibility for the nonclinical safety support of the Lilly Research Laboratories portfolio. Through his accumulated experiences in academia, his career, and his involvement in the Society of Toxicology for over 25 years, Dr. Jones has developed valuable insights into the challenges and opportunities associated with the application of nonclinical safety data in human risk management.

Yasushi Yamazoe, Ph.D, Professor Emeritus, University of Tohoku and Food Safety Commission of Japan

Dr. Yasushi Yamazoe, an Emeritus Professor at Tohoku University in Sendai, Japan and Commissioner, Food Safety Commission, Cabinet Office, for the Government of Japan received the Asia Pacific Scientific Achievement Award. He is a past president of the Japanese Society for the Study of Xenobiotics and has served on the boards of many other scientific organizations. Dr. Yamazoe has enjoyed a long scientific career in drug metabolism and has made significant contributions to the study of the toxicity of drugs and chemicals.

 **Gareth Morgan, M.D., FRCP, FRCPath, Ph.D., Director of the Myeloma Institute for Research and Therapy/University of Arkansas for Medical Sciences (UAMS)**

Seminar: "Genetics of Myeloma"

Dr. Gareth Morgan is an internationally recognized scientist and clinician in the field of molecular genetics in blood cell cancers — in particular, multiple myeloma. He does influential work in characterizing the myeloma genome, defining specific subsets of the disease that have prognostic importance, and developing personalized therapeutic strategies targeted to each subtype. He is also engaged in advanced research in molecular diagnostics, drug development and clinical trials. Within the United Kingdom, he has been instrumental in the implementation of a national cancer policy in terms of governmental initiatives to address myeloma.

Dr. Jufeng Wang, Director, National Center for Safety Evaluation of Drugs/ National Institute for Food and Drug Control (NIFDC) Chinese FDA

Seminar: Current Research Projects in National Center for Safety Evaluation of Drugs

PBPK Model for Assessment of Human Exposure to Bisphenol A

Collaborators at NCTR and Pacific Northwest National Laboratory modified and recalibrated a nonhuman primate, physiologically based pharmacokinetic (PBPK) model for Bisphenol A (BPA) by incorporating human data to reduce uncertainties associated with the model simulations. The new model incorporated experimental data (serum concentration and urinary excretion profiles) from human volunteers who consumed deuterated BPA added in cookies and soup; along with in vitro studies on BPA metabolism in the liver and the small intestine. This model improves human-exposure assessments and reduces uncertainties incurred during

extrapolation across doses and species. A manuscript describing the model is available online at Toxicology and Applied Pharmacology.

For additional information, please contact Jeffrey Fisher, Ph.D. or Xiaoxia Yang, Staff Fellow, Division of Biochemical Toxicology, 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:

Developments for Early Detection of Doxorubicin Cardiotoxicity - http://www.sciencedirect.com/science/article/pii/S0041008X16300266

Early Doxorubicin-Induced Metabolomic Changes in Heart and Plasma - http://onlinelibrary.wiley.com/doi/10.1002/jat.3307/abstract;jsessionid=BBE6DFCFE33B3D004002E6EB575235CF.f03t01

Link to Nanotechnology for Healthcare Conference website - http://rockefellerinstitute.org/institute-programs/nano?source=govdelivery&utm_medium=email&utm_source=govdelivery

NCTR Scientist Recognized with "2016 Transational Impact Award" - http://www.toxicology.org/awards/sot/recipients.asp?source=govdelivery&utm_medium=email&utm_source=govdelivery

Human Infant Intestinal Microbiota as a Reservoir of Antimicrobial Resistance - http://www.nature.com/articles/srep15317

Effects of Silver Nanoparticles on Accumulation, Distribution, and Toxicity - http://toxsci.oxfordjournals.org/content/early/2016/01/04/toxsci.kfv318?source=govdelivery&utm_medium=email&utm_source=govdelivery

Link to “Smart Tots” - http://smarttots.org/?source=govdelivery&utm_medium=email&utm_source=govdelivery

Novel Application of Text Mining Methods to Identify Transcriptional Targets - http://toxsci.oxfordjournals.org/content/early/2016/01/04/toxsci.kfv318?source=govdelivery&utm_medium=email&utm_source=govdelivery

PBPK Model for Assessment of Human Exposure to Bisphenol A - http://www.sciencedirect.com/science/article/pii/S0041008X15301198

NCTR Recent Scientific Publications - http://www.accessdata.fda.gov/scripts/publications/more.cfm?center=NCTR&center_name=Toxicological&source=govdelivery&utm_medium=email&utm_source=govdelivery