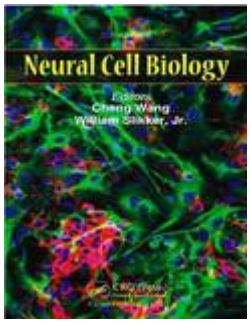
NCTR Quarter Page

Research Highlights, Activities, and Publications
January 2017-March 2017



Book Edited by Recognized Experts from NCTR — Dr. Cheng Wang and Dr. William Slikker, Jr.

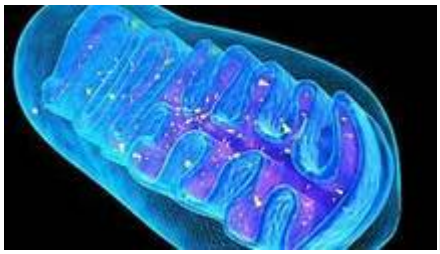
Neural Cell Biology reviews and discusses approaches that can be used as effective tools to dissect mechanisms underlying pharmacological and toxicological phenomena associated with the exposure to drugs or environmental toxicants during development. The book intends to elaborate functional outcomes of component-to-component relationships using rodent and nonhuman primate *in vitro* and *in vivo* models that allow for the directional and quantitative description of the complete organism in response to environmental perturbations. In addition, attention has also been directed to some of the more recent methodologies, including genomics, proteomics and metabolomics, applied in the evolutionary neurobiological field. Preview *Neural Cell Biology*.

Epigenetic Mechanisms in Pathogenesis of Acute Kidney Injury (AKI)

Scientists from NCTR and Texas A&M University have identified an epigenetic mechanism in the pathogenesis of AKI that involves miR-1247 and SOX-9. In kidneys from a mouse alcoholic-liver fibrosis-associated AKI model, miR-1247 is over-expressed and targets Sox9 mRNA resulting in the down-regulation of SOX-9 protein, a key regulator of regeneration. This compromises cellular repair processes and contributes to the severity of AKI. This study suggests that miR-1247 may have value

as a predictive and/or prognostic indicator of AKI severity; and may be a potential target for clinical intervention and management of AKI. A manuscript describing this study is available online at *Toxicology*.

For more information, please contact Igor Pogribny, Ph.D., Division of Biochemical Toxicology.



Effects of Small-Molecule Kinase Inhibitors on Isolated Rat Liver Mitochondria

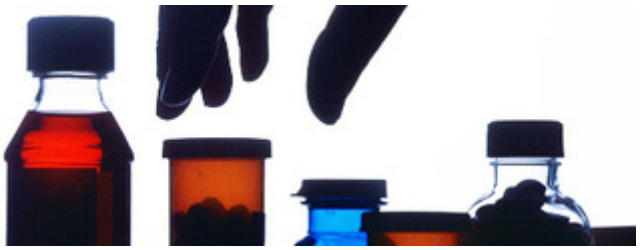
Scientists from FDA's National Center for Toxicological Research and Center for Drug Evaluation and Research used isolated rat liver mitochondria to test 31 FDA-approved small-molecule kinase inhibitors (KIs) for mitochondrial toxicity *in vitro* and showed that only three (all of which are hepatotoxic in humans) caused mitochondrial toxicity at concentrations equivalent to the therapeutic maximal blood concentrations (Cmax). At this concentration, mitochondrial toxicity showed a 100% positive predictive value (PPV) and a negative predictive value (NPV) of 32%. Conversely, at 100-fold Cmax, mitochondrial toxicity had a PPV of 72% and a NPV of 33%. Although *in vitro* mitochondrial toxicity assessments have been proposed as a useful tool to predict the hepatotoxicity of chemicals, these findings suggest that its predictive power for KI-induced hepatotoxicity in humans is limited to positive predictions at Cmax concentrations. A manuscript reporting the results of this study is available online at *Archives of Toxicology*.

For more information, please contact Qiang Shi Ph.D., Innovative Safety and Technologies Branch/Division of Systems Biology or William Mattes Ph.D., DABT, Director, Division of Systems Biology.

FDA Liver Toxicity Working Group Workshop

NCTR hosted the FDA Liver Toxicity Working Group Workshop on January 9, 2017, at Jefferson Laboratories campus in Arkansas with additional online conferencing. The workshop provided a forum for toxicologists, clinicians, and regulators from government, academia, and industry to present and discuss current research from clinical, mechanistic, and *in silico* studies of drug-induced liver injury. The workshop concluded with a panel discussion that addressed the improvement of predictive models and the potential incorporation into regulatory and clinical practice.

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



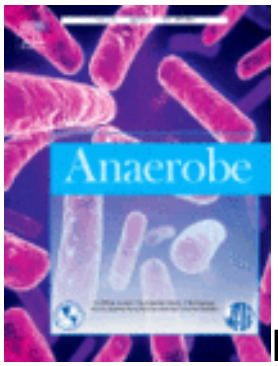
New Technologies to Supplement Animal Studies in Evaluating Drugs for Liver Toxicity Risk

Scientists from NCTR, Merck, and LifeNet Health published a review article in *Institute for Laboratory Animal Research Journal* on several new technological developments that might be used to identify drugs with human drug-induced liver injury (DILI) potential. One of the most critical safety issues confronted in drug development is the risk of causing DILI; particularly when traditional animal studies have sometimes failed to identify drugs that caused liver injury in humans. The authors review the history of this issue and discuss new technologies, such as:

- human cell culture-based systems (e.g., human induced pluripotent stem cell-derived hepatocytes, 3D liver-tissue models, and microfluidic culture systems)
- new animal models (e.g., humanized liver mouse models)
- new translational biomarkers
- computational/predictive models

While these emerging technologies are still in development, many seem to have promise in screening drugs for potential human DILI risk.

For more information, please contact William Mattes Ph.D., Director, Division of Systems Biology.



Effects of β-lactam Antibiotics on Resistance Development and Penicillin-Binding Proteins in *Clostridium perfringens*

NCTR scientists demonstrated that *C. perfringens* — a pathogenic bacterium — rapidly developed resistance to three different classes of β-lactams (penicillin G, cephalothin, and ceftriaxone) and all three antibiotics induced mutation in the penicillin-binding protein (PBP) genes. The largest PBP appeared to be the primary target of β-lactams. These results were consistent with the observed variation in the PBP amino acid sequences found in field isolates of β-lactam-resistant *C. perfringens*. A decrease in the affinity of PBPs for β-lactams is considered a potential mechanism of bacterial resistance to β-lactams. The results of this study are available online at *Anaerobe*.

For more information, please contact Fatemeh Rafii, Ph.D., Division of Microbiology.

Sex and Age Differences in miRNA Expression

NCTR scientists have shown that a set of 214 miRNAs exhibited differential expression in the liver of untreated rats based on age and/or sex. Of the 214 miRNAs, 212 showed age-related differences while 65 showed sex-related differences. In general, miRNA expression was largely stable between sexes and across the rat life span, with the notable exception of 38 miRNAs at 2 weeks of age, which is consistent with early developmental proliferation and differentiation.

As rats mature from adults to old age, miRNAs involved in cell death, cell proliferation, and cell cycle were found to change expression. The results of this study will improve our understanding of epigenetic regulation of hepatic gene expression. Furthermore, these miRNA changes may be a factor in observing differences in age- and sex-dependent susceptibilities to toxicity. This study is available online at *Biology of Sex Differences*.

For more information, please contact James Fuscoe, Ph.D., Director, Personalized Medicine Branch/Division of Systems Biology.

Evaluation of Antimicrobial Effects of Silver Containing Food Contact Materials

NCTR scientists demonstrated that silver-containing food contact materials (FCM) varied in the pattern of silver release into various food simulants and showed slight

effects of delayed growth or no antibacterial activity on the foodborne pathogen, *Salmonella typhimurium* under various food storage conditions that included pH and temperature. The study evaluated total silver content, release capacity, and antibacterial activity of various FCMs, including food-storage containers, food wrapping paper, and a plastic cutting board. The limited antibacterial activity of silver ions leached from FCM was not related to the silver-resistance genetic mechanism, since the tested food pathogen was not positive for such genes.

This study suggests that silver-containing FCMs may not be effective at preventing the growth of common foodborne pathogens. The study is currently available online at *Food and Chemical Toxicology*.

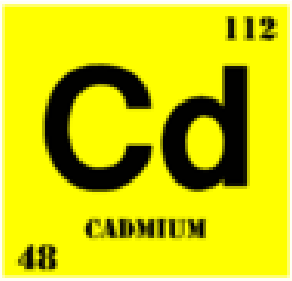
For more information, please contact Sangeeta Khare, Ph.D., Division of Microbiology.

Cadmium Affects Gene Expression During Differentiation of Mouse Embryonic Stem Cells

Scientists from FDA's National Center for Toxicological Research and Center for Drug Evaluation and Research determined the gene-expression profiles of mouse embryonic stem cells (mESCs) during early differentiation under osteoblast culture conditions and demonstrated that exposure to cadmium sulfate inhibited mESC differentiation and disrupted gene expression profiles. Analysis of gene-expression microarrays demonstrated a down-regulation of pluripotency genes, while genes involved in bone and skeletal development were up-regulated over time. Treatment with cadmium, an embryotoxin known to affect multiple organ systems including bone and kidney, resulted in dysregulation of genes involved in skeletal development and renal and reproductive function.

These results suggest that gene-expression analyses may provide sensitive indicators of early mESC differentiation and may improve the predictivity of the mouse embryonic stem cell test (mEST) by identifying potential modes of action for tested chemicals. A manuscript describing this study is available online at *Reproductive Toxicology*.

For more information, please contact Amy Inselman, Ph.D., Biomarkers and Alternative Models Branch/Division of Systems Biology.



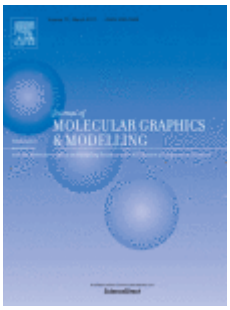
In Vitro to *In Vivo* Extrapolation (IVIVE) for Drug-Induced Liver Injury (DILI)

Preclinical animal-toxicity studies may not accurately predict hepatotoxicity in humans. In light of this, *in vitro* systems have been developed that have the potential to supplement or even replace animal use.

Scientists from NCTR, in collaboration with scientists from Hannover Medical School in Germany and University of Birmingham in UK, conducted an *in vitro* to *in vivo* extrapolation (IVIVE) using gene-expression data. The data was based on rats treated with 131 compounds for 28 days and two i*n vitro* data sets (rat or human primary hepatocytes) treated with the same compounds for 24 hours. A high IVIVE potential was noted for rat primary hepatocytes, whereas the IVIVE potential for human primary hepatocytes was lower, indicating species difference playing a critical role in IVIVE. When limiting the analysis to only those drugs causing DILI, the IVIVE potential was improved for both rats and humans.

The study concluded that rat or human gene-expression data generated *in vitro* could supplement the standard rodent *in vivo* study, particularly for severe hepatotoxic endpoints. This publication is now available online at *ALTEX: Alternatives to Animal Experiments*.

For more information, please contact Zhichao Liu, Ph.D., Division of Bioinformatics and Biostatistics or Weida Tong, Ph.D., Director, Division of Bioinformatics and Biostatistics.



Development of Computational Models of hERG Potassium Channel Binding

NCTR scientists developed a novel computational 3D-SDAR (Three-Dimensional Spectral Data-Activity Relationship) model to predict the ability of a chemical to block the hERG potassium channel. The model was developed and validated using a set of 180 hERG channel inhibitors. It predicted correctly 44 out of the total of 57 drugs and drug derivatives comprising the external prediction set. Importantly, the model identified a three-center toxicophore composed of two aromatic rings and an amino group, which is similar to the toxicophore previously reported for chemicals that lead to phospholipidosis. Drugs in development are screened for hERG binding activity because a number of drugs have been removed from the market due to cardiovascular toxicity related to potassium channel inhibition. A manuscript describing this study is available online at *Journal of Molecular Graphics and Modelling*.

For more information, please contact Iva Stoyanova-Slavova, Ph.D., Innovative Safety and Technologies Branch/Division of Systems Biology.

2017 Mid-South Computational Biology and Bioinformatics Society (MCBIOS) Conference

NCTR scientists presented their work at the 14th Annual MCBIOS Conference held March 23-25, 2017, in Little Rock, Arkansas. The topics of NCTR's presentations included the use of:

- metagenomics to evaluate antimicrobial resistance

- data-mining methods for treatment decisions in precision medicine
- molecular dynamics and quantum mechanical calculations to determine estrogen receptor alpha-binding reaction mechanisms
- next-generation sequencing to evaluate cancer- driver mutations in rat tumors as biomarkers of human carcinogenesis
- *in silico* (QSAR) and biological models (hepatic cell lines, microRNAs) to predict and/or detect drug-induced liver injury.

The regional meeting provides a forum for networking and collaboration between academic, industry, and government scientists in the mid-south region to promote the development and advancement of bioinformatics and computational biology.

NCTR-Developed FDALabel Used as FDA Labeling Review Tool

Hundreds of new or updated human prescription-drug, over-the-counter drug, and biological-product labeling with information about product indications, target populations, and adverse drug reactions are added weekly to the FDALabel database developed at NCTR.

FDALabel is a publicly available database and tool that makes previously unavailable information easy for researchers and FDA staff who review labelings for the safety and effectiveness of drugs to access.

NCTR customized FDALabel for reviewers and other staff from FDA's Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research to perform customizable searches of about 90,000 labeling documents.

FDALabel is very useful for FDA staff who review and/or develop prescribing information, patient labeling, carton/container labeling, and over-the-counter labeling.

Learn more about and get access to FDALabel.

2017 SOT Meeting

The Society of Toxicology (SOT) Annual Meeting is the largest gathering of industry, governmental, and academic toxicologists in the world. There were more than 6,800 attendees at the 2017 Annual Meeting held in Baltimore, Maryland in March. NCTR scientists gave presentations and participated on several symposia. Additionally, Alexandra Folcik received the "Pfizer SOT Undergraduate Award" for research conducted at NCTR.

- Abstract Title: Differential Gene Expression as a Possible Predictor of Susceptibility to Tyrosine Kinase Inhibitors Organ-Specific Toxicities

More 2017 SOT Awards

For recurring updates, visit www.fda.gov/globalsummit.

THEME: Emerging Technologies for Drug and Food Safety

DATE: September 18-20, 2017

LOCATION: Brasilia, Brazil

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

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