U.S. FOOD & DRUG ADMINISTRATION

National Center for Toxicological Research (NCTR)

Systems Biology

About the Division of Systems Biology (DSB)

Division Mission

Address regulatory research needs, knowledge gaps, and emerging health threats using systems-biology approaches and innovative technologies in (1) safety and use of medical products (i.e., drugs, biologics, and devices), (2) safety of foods and supplements, (3) safety and detection of components and impurities in regulated products, and (4) development of technological standards and methods used in regulatory science.

Organization

DSB is comprised of the immediate office and two branches:

- Omics, Models, Imaging and Chemistry Branch (OMIC)
- Innovative Sciences and Technology (IST)

Research Interests

- Mechanisms of Toxicology and Susceptibility to Adverse Effects
- Systems and Organ Toxicities
- Toxicological Effects on Reproduction, Development, and Fertility
- Methodologies, Diagnostics, and Models for Regulatory Science Applications
- Neuropharmacology Metabolomics and Toxicokinetics

Select DSB Accomplishments in 2022

Clinical/Translational Omics Biomarkers

- Qualified protein plasma biomarkers for prediction of anthracycline-associated cardiotoxicity.
- Reported microRNA-34a-5p as an early circulating preclinical biomarker of doxorubicin-induced cardiotoxicity.
- Evaluated the effects of cefoperazone treatment of mice on metabolite activity and gut microbiome.

Predictive Toxicology

- Investigated a Liver-Chip System to predict individual susceptibility and adaptation to drug-induced liver injury.
- Continued development of a human-based in vitro cardiac contractile assay to investigate the role of sex differences to oncologic drugs.
- Developed an SDAR model that was validated by collaborators at NCATS and can be used to identify drug risks that can cause clinical cardiotoxicity due to hERG inhibition.
- Investigated the use of human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) for cardiac safety assessment in nonclinical studies to better understand of the variability of the human-based in vitro system to predict drug-induced cardiotoxicity.

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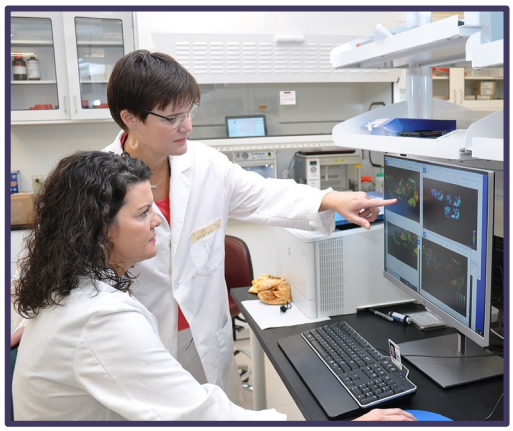
Select DSB Accomplishments in 2022 (Continued)

Therapeutic Safety and Product Center Support

- Investigated opioid-induced neural tube defects in a mouse model.
- Employed mass spectrometry-based metabolomics technologies to assess the effects of high intensity narrow spectrum light on plasma and platelets suspended in plasma.
- Established a mouse tumor model of inflammation to evaluate cytokine release syndrome, neuroinflammation, and neurotoxicity following CAR T-cell therapy.
- Screened central nervous system proteins for potential binding to montelukast.

Response to Health Threats/Emergencies

- Completed SARS-CoV-2 infection studies in a humanized mouse model to evaluate the effects of infection and anti-viral drug treatment during pregnancy.
- Employed imaging mass spectrometry to define the N-glycan profiles of co-localized SARS-CoV-2 and immune cell infiltrates in tissues from COVID-19 patients and mouse models.
- Established a Broad Agency Agreement for a COVID-19 clinical sample biobank.



Ongoing DSB Research Projects in 2023

Clinical/Translational Omics Biomarkers

- Conduct multi-center biomarker qualification study of predictive protein biomarkers of anthracycline-induced cardiotoxicity.
- Evaluate Leishmania parasite vaccine candidates.
- Evaluate cefoperazone-induced changes in metabolic activity in accordance with changes to the gut microbiome of mice.

Predictive Toxicology

- Evaluate new alternative methodology platforms for prediction of hepatoxicity in nonclinical toxicological species and humans.
- Develop and evaluate a folliculogenesis model to assess drug/chemical toxicity.
- Predict adverse events using drug-endogenous ligand-target networks generated using 3D-similarity and machine learning methods.

Therapeutic Safety & Product Center Support

- Assess montelukast exposure in the brain and potential central nervous system binding targets.
- Evaluate CAR T-cell therapy-related acute inflammatory toxicities in vivo, including cytokine release syndrome, neuroinflammation, and neurotoxicity.
- Study cannabinoid neuropharmacology and pharmacokinetics.

Response to Health Threats/Emergencies

- Differentiate patient-specific immune system responses with a systems biology evaluation.
- Assess COVID-19 effects on pregnancy and prenatal and postnatal development.

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