U.S. FOOD & DRUG ADMINISTRATION

National Center for Toxicological Research

Systems Biology

The mission of the Division of Systems Biology (DSB) is to apply systems-biology approaches and innovative technologies to address regulatory research needs, knowledge gaps, and emerging health threats regarding:

- safety and use of medical products (e.g., drugs, biologics, vaccines, and devices)
- safety of foods and supplements
- safety and detection of components and impurities in regulated products
- development of technological standards and methods used in regulatory science

2023 Select DSB Accomplishments

DSB-supported research projects in 2023 incorporated subject matter experts from across the Agency and NCTR, as well as from external collaborating institutions from other government agencies, academia, consortia, and industry. New projects initiated in 2023 resulted from outreach efforts with FDA colleagues at other Centers/Offices, and include studies related to in silico and in vitro new approach methods (NAMs) in predictive toxicology, vaccines, cannabinoids, and biomarker research.

Clinical/Translational Omics Biomarkers

- Received approval of an employee invention report for patent submission for protein biomarkers that were identified and qualified for prediction of anthracycline-associated cardiotoxicity.
- Organized a multi-center study InforMed Prediction of Antracycline-Induced CardioToxicity (IMPACT) to qualify candidate biomarkers of doxorubicin-induced cardiotoxicity.
- Reported the potential role of the apelin-APJ pathway as an early circulating preclinical biomarker of doxorubicin-induced chronic cardiotoxicity (*J Appl Toxicol*).
- Reported identification of potential early-stage prostate cancer biomarkers (*Cancer Genom Proteom*).

Predictive Toxicology

- Conducted qualification studies using liver NAMs, including microphysiological systems, to establish reliability and reproducibility of functional assays and drug-induced toxicities. This work was highlighted at the White House Demo Day in Washington, D.C., FDA Grand Rounds, and the 2023 American College of Toxicology conference. These findings are being used to help regulators evaluate predictability and translation of cellular toxicology observed using NAMs approaches with that of traditional nonclinical toxicology studies and clinical hepatotoxicity.
- Organized a workshop at the 2023 Society of Toxicology (SOT) conference regarding “Moving Stem Cell-Derived New Approach Methods toward Regulatory Acceptance.”
- Organized an FDA study with investigators at multiple FDA Centers to develop a predictive toxicology model for drug placental permeability using 3D-fingerprints and machine learning based on novel empirical data from human-based NAMs with in vivo confirmation.

- Developed ongoing qualification studies to evaluate new alternative models of folliculogenesis for assessing drug/chemical toxicity.

Therapeutic Safety and Product Center Support

- Conducted multiple studies to evaluate concerns of potential drug-induced neuropsychiatric risks associated with the widely used drug montelukast. Ongoing studies include verification of binding potential to candidate protein targets in human neural cells and evaluation of potential for drug accumulation in the brain.

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NCTR supported the global chain of lights as part of the "Light Up for Rare" global event to raise awareness of rare diseases

Accomplishments (Cont.)

- Conducted lipidomic, metabolomic, and proteomic research to support evaluating pathogen-reduced platelet approaches for collaborators at the FDA Center for Biologics Evaluation and Research (CBER), which could serve to establish an alternative and translatable method to secure the integrity of the platelet (PLT) supply and elucidate sensitive markers of PLT stability and degradation.
- Conducted studies to address knowledge gaps regarding toxicological risks of impurities found in oligonucleotide drugs. Evaluation of hepatoxicity of oligonucleotide impurities in human cells using NAMs revealed a greater degree of variability and potential risk than previously anticipated.
- Conducted biomarker studies using metabolomics to characterize immune responses, efficacy, and safety of novel leishmania parasitic vaccines being investigated by CBER collaborators in order to identify potential vaccine candidates for the Orphan indication Leishmaniasis.

Outreach

- Participated in the virtual FDA Rare Disease Day 2023 public meeting. Jessica Hawes Oliphant, Ph.D., Deputy Director of DSB, spoke about the importance of research on and funding for rare diseases and on the work being done at NCTR in support of rare diseases.
- Assisted in organizing **FDA's 2022 Multi-Component Biomarker Workshop** and wrote the associated white paper published in 2023 in *Biomark Med*.
- Led the **Montelukast Working Group**, in coordination with Center for Drug Evaluation and Research review divisions, which responded to numerous external requests from various media and patient advocacy groups seeking information regarding the status of the highly anticipated DSB montelukast studies.
- Played prominent roles in the organization and production of the **First FDA Omics Day** and **FDA's IQ MPS Training Course**.
- Provided an internal consult to Center for Food Safety and Applied Nutrition, reviewing preclinical studies for the potential cardiovascular risk of erythritol.
- Served as Abstract Reviewer for 63rd Annual Meeting for the Society for Birth Defects Research and Prevention.
- Served as a judge for the SOT Reproductive and Developmental Toxicology Specialty Section Best Paper Award.

By the Numbers

66	research protocols supported
65	platform presentations delivered
37	posters presented
17	accomplishment awards
14	scientific conferences attended
12	papers published