FDA

# NATIONAL CENTER FOR TOXICOLOGICAL RESEARCH

# 2023 ANNUAL REPORT

# Contents



*This annual report is best viewed in electronic format (PDF). Throughout the document you will find links to other sections of the report denoted with a page number, links to NCTR pages on FDA.gov, and various referenced scientific publications. If you are reading a hard copy, please visit www.fda.gov/nctrannualreport to access dynamic content.*

# Director's Message

U.S. FOOD & DRUG ADMINISTRATION

National Center for Toxicological Research

***NCTR was established in January 1971 as a non-regulatory national resource to conduct integrated toxicological research and foster interagency, academic, and industrial collaboration in support of risk-assessment needs related to public health. NCTR is co-located on the Jefferson Labs (JL) campus with the FDA Office of Regulatory Affairs Arkansas Human and Animal Food Laboratory.***

**Tucker A. Patterson, Ph.D.**
***NCTR Director***

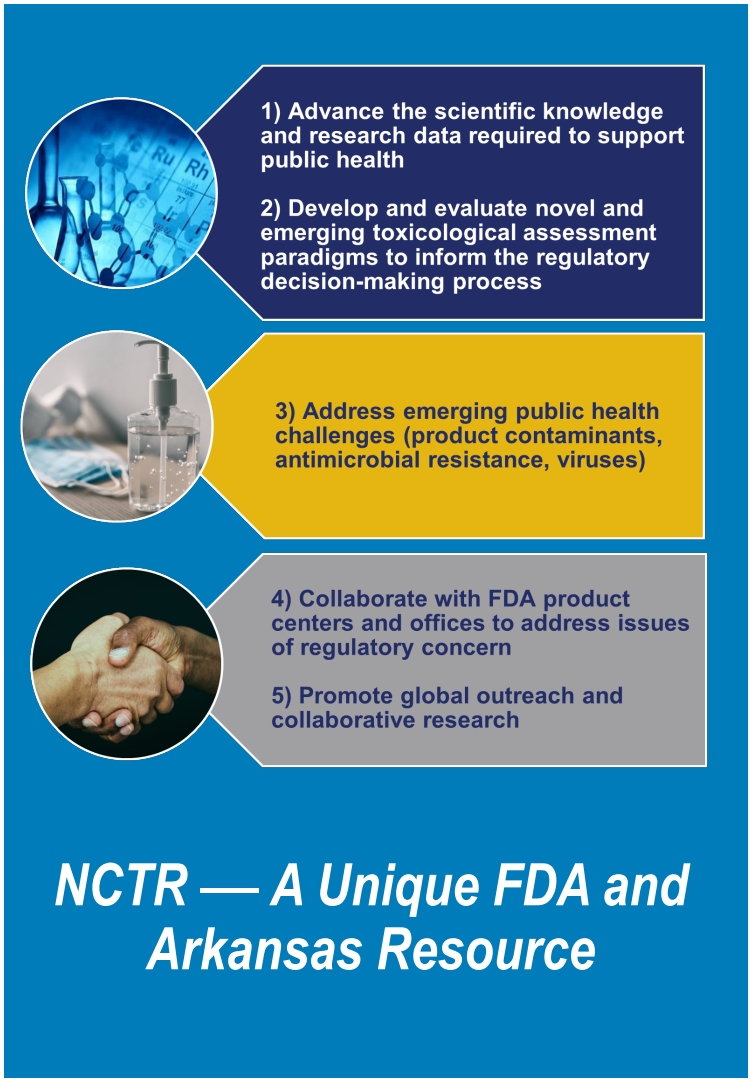
The National Center for Toxicological Research (NCTR), located within the Food and Drug Administration's (FDA) Office of the Chief Scientist, supports FDA's regulatory product centers. Established in 1971, NCTR answers the FDA's need for non-biased, high-quality research accomplished through innovative science-based solutions, comprehensive training, and global collaborations. NCTR continues to survey current landscapes and focus on FDA needs by providing positive contributions, reliable data, and new scientific methods, all of which assist the Agency with its public health mission.

This annual report highlights the outstanding accomplishments of NCTR research scientists. Additionally, this report documents how NCTR scientists continue to support FDA in generating data and advancing innovative tools and approaches that are vital to the Agency's research capability, its ability to predict risk and efficacy, and address emerging issues of concern to public health.

I am excited and privileged to lead the exceptional staff at NCTR. These dedicated public servants strive to support FDA's public health mission and improve the quality of life for everyone.

# About NCTR

- Provides interdisciplinary toxicology research solutions and consultations that support and anticipate future FDA needs to guard and improve personal and public health
- Uses multidisciplinary research teams to develop novel translational research approaches for safety-assessment protocols that provide FDA with faster, more accurate, and economical methods for addressing regulatory questions
- Engages in collaborations with scientists across FDA and other government agencies, industry, and academia to strengthen the scientific foundations vital to developing sound regulatory policy, and to promote the international standardization and global harmonization of regulatory science
- Participates in national and international consortia that provide harmonized standards for technologies and risk-evaluation methods vital to FDA's regulatory and public-health mission
- Provides and encourages multidisciplinary workforce development and fosters national and international collaborations with scientists from government, academia, and industry




## NCTR Mission

Address FDA's needs with high-quality research and serve as a global resource for collaboration, training, and innovative scientific solutions

## NCTR Vision

Conduct scientific research to provide reliable data for FDA's decision-making and develop innovative tools and approaches that support FDA's public health mission

# About NCTR

## Organizational Acronyms

FDA Acronyms and Abbreviations Database

| | |
|---|---|
| **NCTR Offices and Divisions** | |
| DBB | Division of Bioinformatics and Biostatistics |
| DBT | Division of Biochemical Toxicology |
| DGMT | Division of Genetic and Molecular Toxicology |
| DM | Division of Microbiology |
| DNT | Division of Neurotoxicology |
| DSB | Division of Systems Biology |
| OD | Office of the Director |
| OM | Office of Management |
| OR | Office of Research |
| OSC | Office of Scientific Coordination |
| RCRM | Office of Regulatory Compliance and Risk Management |
| **FDA Offices and Centers** | |
| CBER | Center for Biologics Evaluation and Research |
| CDER | Center for Drug Evaluation and Research |
| CDRH | Center for Devices and Radiological Health |
| CFSAN | Center for Food Safety and Applied Nutrition |
| CTP | Center for Tobacco Products |
| CVM | Center for Veterinary Medicine |
| OC | Office of the Commissioner |
| OCS | Office of the Chief Scientist |
| ODT | Office of Digital Transformation |
| OFEMS | Office of Facilities Engineering and Mission Support Services |
| ORA | Office of Regulatory Affairs |
| OWH | Office of Women's Health |
| PHCE | Perinatal Health Center of Excellence |
| **Organizations Outside FDA** | |
| AAALAC | Association for Assessment and Accreditation of Laboratory Animal Care Intl. |
| ARA | Arkansas Research Alliance |
| AR-BIC | Arkansas Bioinformatics Consortium |
| CDC | Centers for Disease Control and Prevention |
| EPA | Environmental Protection Agency |
| HESI/GTTC | Health and Environmental Sciences Instititute/Genetic Toxicology Technical Comm. |
| NCATS | National Center for Advancing Translational Sciences |
| NICEATM | NTP Interagency Center for the Evaluation of Alternative Toxicological Methods |
| NIH, NIEHS | National Institutes of Health, National Institute of Environmental Health Sciences |
| NTP | National Toxicology Program |
| OECD | Organization of Economic Cooperation and Development |
| ORISE | Oak Ridge Institute for Science and Education |
| UAMS | University of Arkansas for Medical Sciences |
| USDA | United States Department of Agriculture |

# About NCTR

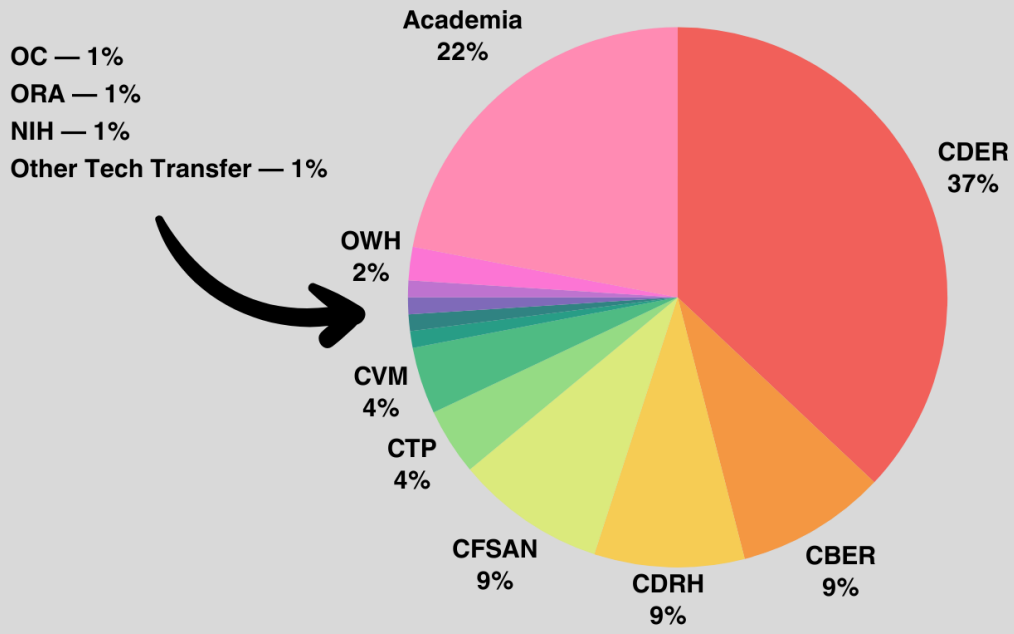
## *Research Protocol Activity*

***By Calendar Year***

| | 2020 | 2021 | 2022 | 2023 |
|---|---|---|---|---|
| Manuscripts | 162 | 144 | 148 | **120** |
| Technical Reports | 61 | 50 | 39 | **70** |
| New Protocols | 48 | 51 | 47 | **41** |

## NCTR Supports FDA Product Centers

### Majority of Protocols are Collaborations



# About NCTR

## Evolving Scientific Areas

- **Artificial intelligence (machine learning, text mining, in silico modeling)**
- **Compounds of concern/rapid response**
- **Microbiome and host interactions**
- **Microorganism detection in FDA-regulated products**
- **New approach methods (NAMs)**
- **Omics (genomics, metabolomics, proteomics, epigenetics)**
- **Perinatal and maternal health**
- **Research addressing unmet needs (minority disparities, rare diseases, at-risk populations)**
- **Translational and precision medicine**

## NCTR Expertise

- **Advanced imaging**
- **Analytical chemistry**
- **Antimicrobial resistance and pathogenicity**
- **Bioinformatics and biostatistics (data mining)**
- **Biomarker development**
- **Genetic toxicology assay development**
- **Guideline studies**
- **Microphysiological systems (MPS) and virtual models**
- **Neurochemistry, neuropathology, and behavioral studies**
- **Physiologically based pharmacokinetic (PBPK) modeling**
- **Reproductive and developmental toxicology**

## *FDA-TRACK*

FDA-TRACK is FDA's agency-wide performance management system that monitors FDA centers and offices through key performance measures and projects. NCTR has several key research projects and other related metrics that are tracked and published in FDA-TRACK, such as GovDelivery subscriptions, research publications measures, and key projects.

### NCTR Key Projects

- Assessing the Effects of Methadone or Buprenorphine and their Combined Use with Cannabinoids on Human Neural Stem Cells — ***ON TRACK***
- Investigating Early Signs of Sex-Difference in Adverse Drugs Effects to Better Protect Women's Health — ***ON TRACK***

***Explore the progress NCTR is making towards its strategic priorities.***

## By the Numbers

| | |
|---|---|
| 1M+ ft$^2$ | 30 buildings |
| 100+ | Experimental Laboratories |
| 75+ | AAALAC Laboratories |
| ~500 | Employees |
| 6 | Research Divisions |
| 5 | Offices |

# Outreach

## 9th Annual Arkansas Bioinformatics Consortium Conference

The theme for the Arkansas Bioinformatics Consortium (AR-BIC) 2023 conference was "Bioinformatics, Big Data, AI (Artificial Intelligence), and Public Health: An Integrated World." Dr. Weida Tong, DBB Director, oversaw the Scientific Program Committee that organized a one-and-a-half-day program and FDA's Chief Scientist, Dr. Namandjé N. Bumpus, provided opening remarks that highlighted current research goals of pursuing new alternative methodologies and helping the public to better understand science.

## 9th Symposium on Antimicrobial Resistance in Animals and the Environment

Multiple NCTR scientists attended the 9th Symposium on Antimicrobial Resistance in Animals and the Environment in Tours, France. The symposium aims to present a global vision of the impact of antibiotic use and resistance in the animal world, its environment, and consecutive repercussion on human health.

## 2023 American College of Toxicology Conference

NCTR staff attended the 44th Annual Meeting of the American College of Toxicology (ACT) in Orlando, Florida, joining a global community of professional scientists representing the pharmaceutical and biotech industries, regulatory agencies, contract research organizations, academia, and consulting firms. The meeting included plenary speakers, professional networking events, a poster session, and an awards ceremony and allowed researchers from NCTR the opportunity to exchange ideas with toxicologists, industry consultants, and other professionals.

## Arkansas Research Alliance

### ARA Project Scope

Laura Schnackenberg, Ph.D., DSB Director and Arkansas Research Alliance (ARA) Academy member, presented the ARA Project Scope in May 2023. Dr. Schnackenberg discussed her division's research in alternative methods of drug testing including tissue chips.


*Click to watch Dr. Schnackenberg's presentation* ▶

### ARA Academy of Scholars and Fellows

Igor Pogribny, M.D., Ph.D., a research biologist in NCTR's DBT, was formally inducted as a new fellow of the ARA Academy of Scholars and Fellows on August 10, 2023. Highlighted by a special welcome and recognition from Arkansas Governor Sarah Huckabee Sanders, he was one of seven new members welcomed during the ceremony at the Arkansas State Capitol. Dr. Pogribny was selected to join the ARA Fellows program that recognizes research leaders with an established history of impact.

*Left to Right: Bryan Barnhouse, ARA President and CEO; Dr. Tucker Patterson, NCTR Center Director; Arkansas Governor Sarah Huckabee Sanders; Dr. Igor Pogribny, NCTR scientist being inducted as an ARA Fellow; and Ritter Arnold, Chair of the ARA Board of Trustees, during the ceremony at the Arkansas State Capitol*

# Outreach

## FDA Grand Rounds


The FDA Grand Rounds is an educational presentation that is webcast monthly to highlight cutting-edge research underway across the Agency and its impact on protecting and advancing public health. Each session features an FDA scientist presenting on a key public health challenge and how FDA is applying science to its regulatory activities. The 45-minute educational presentation is followed by questions from the audience.

In 2023, three Grand Rounds sessions were presented by NCTR researchers.

- The Plasmid Puzzle—Finding Solutions in *Salmonella* (Dr. Kristina Feye)
- Electron Microscopy—Still a Powerful Research Tool (Dr. Angel Paredes)
- Microphysiological Systems as Novel Disease Models and Drug Development Tools (Drs. Dayton Petibone and Qiang Shi)

## FDA Omics Days

The 2023 FDA Omics Days featured speakers from industry, academia, and government, including NCTR, to discuss omics technologies, data integration, and data management.

### NCTR Participation in 2023 FDA Omics Days

**Breakout Session — *Genomics, Transcriptomics, Metagenomics***
Q&A Panel (Dr. Javier Revollo)

**Breakout Session — *Proteomics and Metabolomics***
Q&A Panel (Dr. Richard Beger)

**Breakout Session — *Data Integration and Data Management***
Q&A Panel (Dr. Vikrant Vijay)

**Poster Sessions**
**Links to posters are PDF downloads*

- "Assessment of Plasmids for Relating the 2020 *Salmonella enterica* Serovar Newport Onion Outbreak to Farms Implicated by the Outbreak Investigation"
- "Evaluating Renal Pathology in Post-COVID-19 Human Autopsy Tissues"
- "Evaluation of Plasma Proteome and miRNA Changes Related to COVID-19 Patient Severity Response"
- "MALDI Imaging Mass Spectrometry of Mouse Fetuses to Assess Markers of Neural Tube Defects After Maternal Opioid Exposure"
- "Lipidomics Evaluation of the Impact of Fentanyl Treatments on Neural Stem Cells"
- "Lysophosphatidylcholine Mediates Neutrophil Activity Through Early Metabolic Modulation Following Immunization with a Live-Attenuated Leishmania Vaccine"
- "Metabolomics Evaluation of the Photochemical Impact of Violet-Blue Light (405 nm) on Ex Vivo Platelet Concentrate"
- "Proteomic Profiling Reveals Antibiotic Resistance Mechanisms in *Staphylococcus epidermidis* Biofilms under Tigecycline Pressure"

# Outreach

## FDA Science Forum


The FDA Science Forum offers an exciting opportunity for the public to view the collaborative efforts of FDA's 11,000 scientists, including NCTR scientists, and covered topics including use of real-world evidence, complex innovative trial design, artificial intelligence (AI) and big data, medical countermeasures, and technologies to support pathogen reduction. ***View NCTR poster presentations***.

### NCTR Participation in FDA 2023 Science Forum

**Concurrent Session 2 — *Product Development Tools and Manufacturing***

- "Opportunities and Challenges in Using Liver Microphysiological Systems to Study Drug Metabolism and Hepatotoxicity" (Dr. Qiang Shi)

**Concurrent Session 4 — *Tools to Effectively Use Big Data***

- Panel Discussion (Dr. Joshua Xu)

**Concurrent Session 5 — *Food and Cosmetic Safety***

Chair/Moderator (Dr. Raj Nayak)

- "Studies to Assess the Virulence of Enteric Foodborne Pathogens" (Dr. Steven Foley)
- "An Update on NCTR and Office of Cosmetics and Colors' Collaborative Efforts to Support Cosmetics Safety Evaluation" (Dr. Luísa Camacho)
- Panel Discussion and Q&A

**Concurrent Session 6 — *Medical Countermeasures, Infectious Disease, and Pathogen Reduction Technologies***

Chair/Moderator (Dr. Mugimane Manjanatha)

- Introduction (Dr. Mugimane Manjanatha)
- "Evaluation of Testicular Organoids as a Model for Zika Virus Infection" (Dr. Dayton Petibone)
- Panel Discussion and Q&A

**Concurrent Session 7 — *Advancing Products Based on Novel Technologies***

Chair/Moderator (Dr. Mugimane Manjanatha)

- "Host-Microbiome Crosstalk: Disruption of Gastrointestinal Barrier as Toxicity Assessment Tool" (Dr. Sangeeta Khare)
- Panel Discussion and Q&A

## FDA Scientific Computing Days


FDA's 11th Annual Scientific Computing Days (SCD) was hosted by FDA Scientific Computing Board, CTP, NCTR, and National Cancer Institute. This year's public SCD theme was "Sharing and Collaboration in the Data Multiverse: Scientific Computing for Public Health Solutions" and included keynote and guest speakers, a poster gallery, and various breakout sessions. Denny Skiles, Associate Director of the Office of Management, served as SCD co-chair. NCTR researchers served as session organizers and poster presenters.

### NCTR Participation in FDA 2023 Scientific Computing Days

**Breakout Session — *Artificial Intelligence's Impact on FDA***
(Dr. Donna Mendrick, organizer)

**Breakout Session — *Large Language Models in Play***
(Dr. Liang Zhao, organizer)

- Presentation: "An Introduction to Large Language Models and Their Potential in FDA Review Process" (Dr. Jae Hyun Kim)

**Poster Sessions**

**Links to posters are PDF downloads*

- "Modifying the Charlson Comorbidity Index for the American Indian Population Using the Strong Heart Study Data"
- "TransOrGAN: An Artificial Intelligence Mapping of Rat Transcriptomic Profiles between Organs, Ages, and Sexes"
- "A Systematic Analysis and Data Mining of Opioid-Related Adverse Events Submitted to the FAERS Database"

# Outreach

## Global Summit on Regulatory Science

The 13th Global Summit on Regulatory Science (GSRS23) was held in Parma, Italy, September 27-28, 2023, with pre-meeting workshops on September 26. GSRS23 is co-hosted by the European Food Safety Authority (EFSA) and Global Coalition for Regulatory Science Research (GCRSR), which is comprised of regulatory-science leaders from around the world. The theme for GSRS23 was "Emerging Technologies and Their Role in Regulatory Application." There were workshops and platform presentations from scientists representing Belgium, Brazil, Canada, China, Denmark, EU, France, Hungary, Italy, Japan, Netherlands, Singapore, United Kingdom, and the United States.

**GSRS23 Highlights**

- Recorded message from the FDA Commissioner, Dr. Robert M. Califf
- Welcome and Opening Session 1 with NCTR Center Director, Dr. Tucker Patterson (Session 1 co-chair)
- Horizon Scanning Session 7 with retired NCTR Center Director, Dr. William Slikker, Jr. (Session 7 co-chair)
- Pre-meeting Workshop 1 on nanotechnology supporting NAMs in the food sector and characterization of nanoplastics with Dr. Anil Patri (Workshop 1 co-chair)
- Pre-meeting Workshop 2 on present and future of AI with Dr. Weida Tong
- AI/Machine Learning Session 5 with Dr. Weida Tong (Session 5 co-chair)
- A question-and-answer session during Session 5 on the progress of GCRSR Interagency Large Language Models Taskforce with Dr. Joshua Xu
- Closing remarks by Dr. Weida Tong

**A paper summarizing the GSRS21 conference was published in May 2023 in *Regulatory Toxicology and Pharmacology*.**


*Dr. Tucker Patterson delivered the welcome and opening session at GSRS23*

## NanoDay Symposium

NCTR researchers participated in the 2023 NanoDay Symposium: Continuous Manufacturing of Nanomaterials along with scientists from other FDA centers, academia, and industry. Anil Patri, Ph.D., Director of the NCTR/ORA Nanotechnology Core Facility, welcomed the participants to the public event. Topics discussed during the symposium included the following:

- CDER's experience with approving solid oral drug products benefitting from continuous manufacturing technologies
- Case-studies of intramural and extramural research in the areas of nanomaterials and continuous manufacturing
- Possibilities for industry, academia, and other regulatory agencies to collaborate and engage with FDA in advancing the fields of nanotechnology and continuous manufacturing

**2023 NanoDay**

FDA's 2023 NanoDay Symposium was held in October 2023 and was open to the public.

- *2023 NanoDay Symposium – Part 1*
- *2023 NanoDay Symposium – Part 2*
- *2023 NanoDay Symposium – Part 3*

# Outreach

## Science Advisory Board to NCTR

The Science Advisory Board (SAB) to NCTR advises the NCTR Director in establishing, implementing, and evaluating the research programs that assist the FDA Commissioner in fulfilling his or her regulatory responsibilities. The Board provides an extra-agency review in ensuring that the research programs at NCTR are scientifically sound and pertinent.

*More information on the 2023 SAB meeting can be found on the website.*

### 2023 SAB Meeting

NCTR's 2023 SAB meeting was held virtually in April 2023 over two days.

*Watch Recording of SAB – Day 1*

*Watch Recording of SAB – Day 2*

## Society of Toxicology's 62nd Annual Meeting and ToxExpo

The Society of Toxicology's (SOT) 62nd Annual Meeting and ToxExpo was held March 19–23, 2023 in Nashville, Tennessee. FDA's Chief Scientist, Dr. Namandjé N. Bumpus, kicked off the conference with her opening plenary presentation titled "Advancing Single Cell Technologies in Toxicology." The conference featured a variety of exciting and informative events, including symposium, poster, and exhibitor-hosted sessions on a wide range of toxicological research and technologies. Platform and poster presentations by NCTR research scientists showcased the latest innovative research conducted at NCTR using state-of-the-art methodologies. NCTR hosted a booth at the ToxExpo, providing another platform to facilitate communication and collaboration. The booth was well-organized—with pull-up banners, handouts, and live demos—and staffed with the center's scientists and communication and human resources specialists.


*NCTR leaders, researchers, and staff attended the 2023 SOT Annual Meeting and ToxExpo*

### NCTR Participation in SOT 2023

**Platform Session — *Enhancing Toxicology with Machine Learning***

- "PathologAI – a deep learning framework for whole slide classification in preclinical pathology" (Dr. Joshua Xu)

**Platform Session — *Exploring Time and Cell Diversity in Toxicogenomics Space***

- "Effect of Food-Grade Titanium Dioxide on DNA Methylation in Human Cells" (Dr. Carlos Wells)

**Workshop Session — *Moving Stem Cell-Derived New Approach Methods Toward Regulatory Acceptance***

Chair (Dr. Li Pang)

- "Predicting Interindividual Variability of Doxorubicin Cardiotoxicity with Induced Pluripotent Stem Cell-Derived Cardiomyocytes"

**Workshop Session — *Understanding the Concept of Similarity and its Applications to Toxicological Research and Risk Assessments***

- "Structure similarity based on chemical descriptors, fingerprints, and structural alerts" (Dr. Huixiao Hong)

**Poster Sessions**

- DBT – 10 posters
- DBB – 18 posters
- DGMT – 11 posters
- DM – 1 poster
- DNT – 8 posters
- DSB – 4 posters

# Research Focus Areas

## Antimicrobial Resistance

Antimicrobial resistance (AMR)—the ability of a microorganism (bacteria, virus, fungi, parasite) to resist the effects of a drug—has become a substantial public health concern in recent years. According to the Centers for Disease Control and Prevention (CDC), more than 2.8 million antimicrobial-resistant infections occur in the U.S. each year, and more than 35,000 people die as a result. Because AMR remains a global public health threat, it is one of FDA's Focus Areas of Regulatory Science.

NCTR and its research partners are leading the way in FDA's mission to research, monitor, and respond to AMR concerns across the country with a One Health focus. These actions ensure that the utmost care is taken to protect and promote the health of humans, animals, plants, and the environment.

***Check out scientific posters that discuss some of the AMR-related research at NCTR.***

### Collaborating with CVM to Combat AMR

NCTR works closely with CVM on plasmid research, developing tools to combat AMR (***page 24***, ***page 25***), and discussing the research data with other government agencies through scientific work groups.

One such tool is the publicly available *Salmonella* Virulence Gene Database being used by scientists within FDA, USDA, and other external partners. NCTR scientists developed and optimized databases and matching algorithms to identify *Salmonella* virulence factors from whole-genome sequencing data. The *Salmonella* Virulence Gene Database was used to analyze the genetic diversity, AMR, and virulence determinants of *Salmonella Kentucky* isolates from humans, food animal intestines, retail meat, poultry products, imported foods and food products, and other samples.

## Artificial Intelligence and Bioinformatics

### Artificial Intelligence

NCTR recognizes the variety of regulatory science applications that could benefit from AI, as well as its predictive potential. Using advanced AI technologies, NCTR's bioinformatics scientists have the ability to both compile unique FDA datasets and design AI applications specific to each product center's needs. These capabilities may serve to improve public health and expedite FDA review.

In 2023, NCTR scientists developed RxBERT, an AI model optimized to better understand human prescription drug labeling. They also supported CDER regulatory missions by:

- Improving the accuracy and timeliness of the Novel Drug Approvals Dashboard by creating software to identify new and updated information in the Data Analysis Search Host Database of marketing application information derived from CDER-generated regulatory documentation.
- Completing population of a searchable Executive Carcinogenicity Assessment Committee (ECAC) database within the Smart Template System that allows pharmacology/toxicology reviewers to search ECAC meeting minutes from 1995 to present for information relevant to their current reviews.

***2023 AI/ML Publications by NCTR Researchers***

- **AnimalGAN** — *Nat Commun*
- **SafetAI** — *Regul Toxicol Pharm*
- **BERTox** — *Exp Biol Med*
- **PathologAI** — *Chem Res Toxicol*

### FDALabel

- Updated FDALabel to version 2.8 with new features focusing on interface improvements and search capability enhancements to make the tool more user-friendly and resourceful. This is a collaborative project with NCTR's OSC, NCTR's DBB, and FDA's CDER.

- Hosted the 2nd Annual FDALabel Training for 690 participants. This two-day, FDA-wide virtual training event provided an overview, demonstrations, and real-world applications of FDALabel.

***Read more information on AI, FDALabel, and Bioinformatics Tools.***

# Research Focus Areas

## Cannabis-Derived Products

### Effects of Cannabidiol on Male Reproductive Health

Cannabidiol (CBD), one of the major components extracted from the plant *Cannabis sativa* L., is an FDA-approved drug that treats specific types of seizures. CBD use has become popular within the general population in recent years due to its purported health benefits and increased availability. However, there are uncertainties regarding the safety of CBD, including reproductive toxicity. NCTR scientists in DBT and DGMT, along with FDA's OC and CFSAN, examined the effects of CBD and its two main metabolites (7-carboxy-CBD and 7-hydroxy-CBD), on primary human testicular Leydig cells in vitro. This work was reported in *Arch Toxicol*.

***DBT researchers published a second paper on CBD and presented two posters at the SOT 2023 annual meeting regarding CBD toxocity.***

### Exploring Perinatal Effects of Purified Cannabidiol

A comprehensive study addressing potential developmental neurotoxicity of purified CBD was completed by DNT staff in 2023. Data resulting from this study was presented at the 2023 SOT annual meeting. Pups were exposed to CBD starting in pregnancy (gestational day 6) until 21 days after birth. Results suggested that perinatal CBD exposure did not induce perpetual changes in motivation, working memory or time perception. No significant biochemical alterations were observed in brains of pups exposed to different doses of CBD used in this study.

### Studying the Interactions Between Cannabinoids and Opioids

When performing animal studies, scientists typically focus on the effects of a single substance at a time. However, this is not reflective of real-life situations where people often expose themselves to a host of substances at once. This is particularly true of opioids, as most opioid users also use cannabinoids. Realistically, it is not possible to model all the potential use scenarios in animals. However, by using cell-based models, we can begin to understand how drugs might interact and if co-administration of drugs could amplify their toxic effects. DNT researchers are currently using human neural stem cells to understand the interactions between opioids and cannabinoids on the developing brain. While this project is ongoing, it has already produced important data about the relative toxicity of key metabolites of CBD which will impact interpretation of rodent studies.

## Nanotechnology

### Nanotechnology Accomplishments

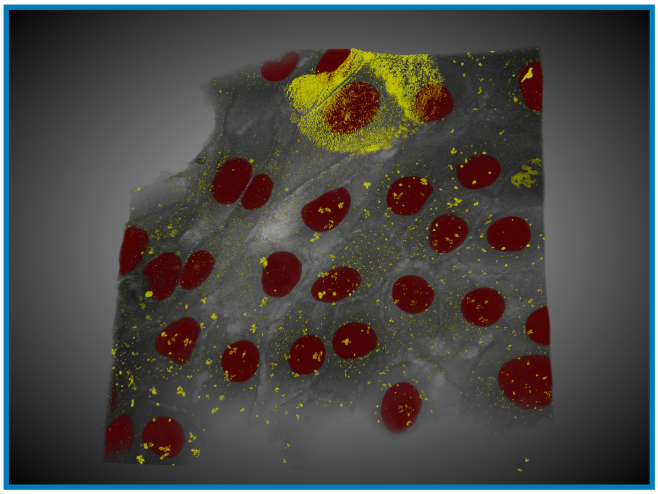
In 2023, the NCTR Nanotechnology Core Facility (NanoCore) (***page 30***) completed two key projects:

- Evaluation of the migration and toxic potential of silver nanoparticles in feminine hygiene products
- Investigation into reported differences in Doxil and generic liposomal doxorubicin products

### Scientific Breakthroughs/Highlights

U.S. EPA released the draft strategy "National Strategy to Prevent Plastic Pollution," which includes ambitious actions to eliminate the release of plastic and other waste from land-based sources into the environment by 2040. NCTR's NanoCore developed a baseline reference dataset of most common polymers present in the environment that would serve towards the development of a collaborative, global, comprehensive, and curated public database for the identification and quantitation of various micro/nano plastics and mixtures (*NanoImpact*).

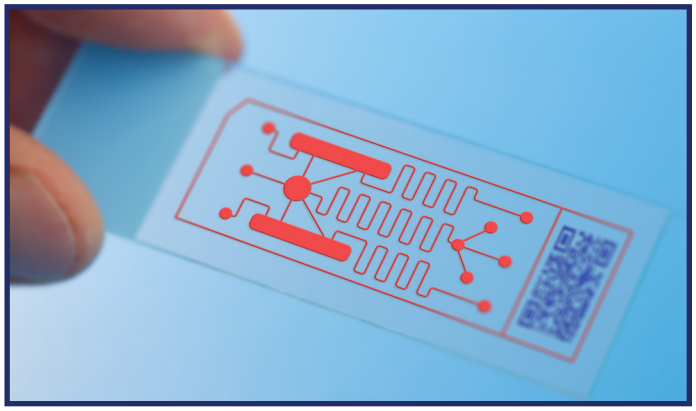
***Read more information about Nanotechnology at FDA and NCTR.***



***A Serial Block Face Scanning Electron Microscopy (SBF-SEM) image showing cells, nuclei (red color) and nanomaterial (yellow). This 3-dimensional imaging and structural analysis is possible with SBF-SEM at the NanoCore, and is available to collaborators utilizing computer-learning software analysis. (Courtesy: Drs. Angel Paredes and Tariq Fahmi).***

# Research Focus Areas

## New Approach Methods



### A New Approach Methodology for Evaluating Germ Cell Mutation

DGMT scientists have established a *Caenorhabditis elegans* (worm) model to evaluate mutagenicity in germ cells. Using known mutagens, they evaluated mutagenic susceptibility of different stages of germ cell development in *C. elegans* using whole genome sequencing. These results suggest that *C. elegans* can be a less expensive and animal-friendly NAM alternative to traditional rodent models for studying germ line mutations. A publication in *Arch Toxicol* describes this work in detail.

### Using New Approach Methodoligies to Evaluate Hepatoxicity of Oligonucleotide Drugs

DSB researchers conducted studies to address knowledge gaps regarding toxicological risks of impurities found in oligonucleotide drugs, supporting CDER's Office of Pharmaceutical Quality. Evaluation of hepatoxicity of oligonucleotide impurities in human cells using NAMs revealed a greater degree of variability and potential risk than previously anticipated. This work may help guide regulatory decisions regarding control of impurities for generic oligonucleotide products and was shared at the 2023 ACT conference.

### Comparing Existing Skin Models with New Alternative Models

DBT researchers authored "Parallel evaluation of alternative skin barrier models and excised human skin for dermal absorption studies in vitro" in *Toxicol in Vitro*. In this study, an experimental workflow is proposed to help compare the performance of alternative skin models with that of excised human skin and understand the potential of each skin model to predict human exposure to topical chemicals of interest to the FDA.

***2023 NAMs Publications by NCTR Researchers***

- "Computational Modeling for the Prediction of Hepatotoxicity Caused by Drugs and Chemicals." In: *Machine Learning and Deep Learning in Computational Toxicology* (Chapter 23)
- "Gaps and Challenges in Nonclinical Assessments of Pharmaceuticals: An FDA/CDER Perspective on Considerations for Development of New Approach Methodologies." *Regulatory Toxicology and Pharmacology*
- "Machine Learning and Deep Learning Promotes Computational Toxicology for Risk Assessment of Chemicals" In: *Machine Learning and Deep Learning in Computational Toxicology* (Chapter 1)
- "Machine Learning for Predicting Organ Toxicity." In: *Machine Learning and Deep Learning in Computational Toxicology* (Chapter 22)
- "Parallel Evaluation of Alternative Skin Barrier Models and Excised Human Skin for Dermal Absorption Studies in Vitro." *Toxicology in Vitro*
- "TransOrGAN: An Artificial Intelligence Mapping of Rat Transcriptomic Profiles between Organs, Ages, and Sexes." *Chemical Research in Toxicology*

## Opioids

NCTR, in collaboration with CDER and NCATS, published a paper providing insight into opioid receptor binding activity to create potentially safer opioid-like compounds. According to the paper in *Int J Mol Sci*, 6,984 opioid-related deaths occurred in 1999 and significantly increased to 94,371 by 2020. These statistics highlight the ever-increasing safety concern of opioid pain medications and show the need for drug makers to develop safer alternatives. This publication is part of a larger research project to create an Opioid Agonists/Antagonists Knowledgebase to assist review and development of analgesic products for pain management and opioid use disorder treatment.

# Research Focus Areas

## Perinatal and Maternal Health

The Perinatal Health Center of Excellence (PHCE) was established by NCTR in 2018 to address existing knowledge gaps in regulatory science covering the perinatal period, which covers pregnancy, childbirth, and infant/child development. This type of research covers a broad range of topics from chemical toxicology to advanced computational modeling and new alternative models, with the purpose of improving perinatal safety and efficacy.

Numerous findings from PHCE-funded studies were published in scientific journals in Fiscal Year (FY) 2023:

- Persistent tissue-specific immunity to SARS-CoV-2 in the upper respiratory tract of children
- Comprehensive risk assessment of infant drug exposure from human milk
- Role neonatal Fc receptor plays in Zika virus infection
- AI-enabled devices for pediatric use

***A list of selected publications and topics related to PHCE-funded research can be found on FDA.gov/nctr.***

***2023 PHCE Select Accomplishments***

- 13 first-year projects funded in FY2023 and continued in FY2024
- 4 second-year projects concluded in FY2023
- 3 first-year projects funded in FY2024
- Principal Investigators represented CBER, CDER, CDRH, and NCTR
- 17 articles published in Calendar Year 2023

***Read more about NCTR's research focus areas.***

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

## Rare Diseases

NCTR conducts research in support of FDA's efforts to generate data focused on underserved populations such as those with rare diseases. A rare disease is defined as any disease or condition that affects fewer than 200,000 persons in the U.S. There are an estimated 7,000 rare diseases, with a public health impact that affects more than 25 million Americans and many millions more of family members in the U.S.

- Jessica Hawes Oliphant, Ph.D., Deputy Director of DSB, participated in the virtual FDA Rare Disease Day 2023 public meeting. She 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.
- NCTR scientists collaborated with CBER and CDER to investigate rare diseases like myelodysplastic syndromes, which are a rare group of blood cancers resulting from altered development of blood cells within bone marrow. The focus of this work is on developing a targeted, error-corrected next generation sequencing (ecNGS) panel to quantify myeloid neoplasm-associated genetic mutations. This work will continue into FY2024.

# Office of the Director/Office of Research

## 2023 OD Select Outreach Events, Presentations, and Publications

### *Tucker A. Patterson, Ph.D. — NCTR Director*

- Presented at the HHS-OWH Endocrine Disrupting Chemicals and Women's Health Symposium
- Served as co-chair — NAMs Global Landscape session at GSRS23 (***page 11***) held in Parma, Italy and hosted by EFSA

### *Gonçalo Gamboa da Costa, Ph.D. — Senior Science Advisor*

- Presented "FDA Research on Xylazine" at the Reagan-Udall Foundation Public Meeting: Mitigating Risks from Human Xylazine Exposure
- Served as panelist — *Addressing the Drug Overdose Crisis: Translational Research and Data Surveillance Communities*; National Academies of Science, Engineering, and Medicine Meeting of Opportunity: Sharing Perspectives on the Substance Use and Overdose Epidemic
- Served as co-organizer — *Trust Your Gut: Establishing Confidence in Gastrointestinal Models* workshop, NIH

### *Donna Mendrick, Ph.D. — Associate Director for Regulatory Activities*

- Presented update on the Alternative Methods Working Group to the FDA Senior Science Council
- Served as keynote speaker and presented "Advancing New Alternative Methods at FDA" (*PDF download*) at the MPS World Summit 2023 held in Berlin
- Presented "Animal Microphysiological Systems: Translation and Other Uses" to the Innovation and Quality Microphysiological Systems (IQ MPS)/FDA workshop (Invitation only)
- Presented "Animal Microphysiological Systems: Translation and Other Uses" to the Tox21 meeting (Closed meeting)
- Served as panelist — *Catalyzing Development and Use of Novel Alternative Methods,* NIH meeting
- Served as chair of the following:
  - » FDA Alternative Methods Working Group (13 seminars)
  - » FDA Artificial Intelligence Working Group (17 seminars)
  - » Breakout session on "Artificial Intelligence's Impact on FDA" at 2023 FDA Scientific Computing Days

## NCTR Research Offices and Divisions

- **Division of Biochemical Toxicology**
- **Division of Bioinformatics and Biostatistics**
- **Division of Genetic and Molecular Toxicology**
- **Division of Microbiology**
- **Division of Neurotoxicology**
- **Division of Systems Biology**
- **Office of Scientific Coordination**

### *2023 Select OD Publications*

- "Machine Learning for Predicting Organ Toxicity."
  In: *Machine Learning and Deep Learning in Computational Toxicology* (Chapter 22)
- "Gaps and Challenges in Nonclinical Assessments of Pharmaceuticals: An FDA/CDER Perspective on Considerations for Development of New Approach Methodologies." *Regulatory Toxicology and Pharmacology*
- "Preface: 2022 International Conference on Neuroprotective Agents." *Experimental Biology and Medicine*

# Division of Biochemical Toxicology

***NCTR's Division of Biochemical Toxicology (DBT) conducts fundamental and applied research designed to define the biological mechanisms of action underlying the toxicity of FDA-regulated products, as well as characterizes the carcinogenic risks associated with chemicals of interest to the FDA.***

**DBT Leadership**

*Division Director – Frederick A. Beland, Ph.D.*
*Deputy Director – Luísa Camacho, Ph.D.*

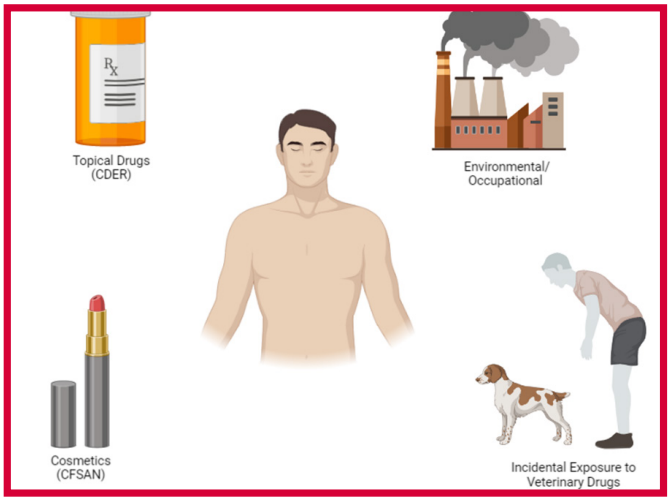
## 2023 DBT Select Accomplishments

### *The Toxicity of Triclosan*

DBT scientists completed a two-year mouse bioassay elucidating the chronic dermal toxicity/carcinogenicity of triclosan. Triclosan is a widely used bacteriostatic and bactericidal agent that is present in a variety of personal care, consumer, and industrial products. Due to its extensive use, there is potential for humans in all age groups to receive lifetime exposures to triclosan, yet data on the chronic dermal toxicity/carcinogenicity of triclosan were lacking. This research, funded by an interagency agreement (IAA) between FDA and the NIEHS, helped address a data gap identified by FDA to assess the risk to humans from dermal exposure to triclosan and contributed to the understanding of the mechanisms of triclosan-associated toxicities. A publication is anticipated in early 2024.

### *Skin Permeation Study of FDA Regulated Products*

Skin permeation is a primary consideration in the safety assessment of cosmetic ingredients, topical drugs, and human users handling veterinary medicinal products. As the need for dermal absorption studies in dermatological product safety assessments grows, so does the impetus to reduce, refine, and replace (Three Rs) the use of animals in regulatory science. Researchers from NCTR's DBT, in collaboration with scientists from FDA's CDER, CFSAN, and CVM, NCATS, and the NICEATM, developed a standardized method to evaluate the suitability of alternative skin barrier models to predict skin absorption in humans. This novel multiparametric experimental approach has broad adaptability to enable the evaluation of existing and future alternative skin barrier models. This work was published in *Toxicol in Vitro* and was sponsored by an FDA Chief Scientist Challenge Grant.




### *Breakthrough in the Study of Nonalcoholic Fatty Liver Disease*

Nonalcoholic fatty liver disease (NAFLD) has grown in global frequency to become the most common chronic liver disease, with a prevalence ranging from 25% to 48% in adults and from 8% to 12% in children. Current evidence indicates the existence of substantial interindividual heterogeneity in susceptibility to NAFLD and its severity. NCTR investigators, in collaboration with scientists from FDA's CDER and Texas A&M University, demonstrated that extensive alterations in the expression of disease-related genes are a fundamental feature of the pathogenesis of NAFLD using a genetically diverse Collaborative Cross mouse population. These findings were published in the *Am J Physiol Gastrointest Liver Physiol*.

### *DBT Research Backs up FDA Regulations*

Research conducted by DBT scientists provided important new data to support an FDA proposal to amend regulations revoking authorization for the use of brominated vegetable oil (BVO) in food due to safety concerns. BVO is a food additive used primarily to help emulsify citrus-flavored soft drinks, preventing them from separating during distribution. The rodent safety studies conducted by NCTR were published in 2022 and confirmed previous reports that dietary exposure to BVO is toxic to the thyroid and results in bioaccumulation of lipid-bound bromine in the body at doses relevant to human exposure.

# In 2023, DBT Scientists

*In 2023, DBT scientists contributed to or participated in the following outreach events:*

## Awards

- Received **FDA Scientific Achievement Award:** Chief Scientist Publication Award for Translational or Applied Science
- Received **NCTR Group Recognition Award** for the rapid and thorough review conducted by the NCTR Monograph team in response to the request made by CDRH
- Received **NCTR Scientific Achievement Award**: Director's Publication Award for Laboratory Science for assessing male reproductive toxicities induced by CBD and its main metabolites
- Received two **NCTR Special Act Awards**: For outstanding efforts in ensuring the success of the NCTR Summer Student Research Program (SSRP) and providing mentorship to college students

## Memberships

- 62nd Annual SOT Meeting (session chair)
- External Advisory Board, Masonic Cancer Center, University of Minnesota (member)
- FDA Diversity, Equity, Inclusion, and Accessibility Committee (DEIA) – Team 4
- International Agency for Research on Cancer Working Group to Evaluate the Carcinogenic Hazards to Humans (aspartame, methyl eugenol, and isoeugenol), Experimental Carcinogenesis Subgroup (chairman)
- International Agency for Research on Cancer Working Group to Evaluate the Carcinogenic Hazards to Humans (perfluorooctanoic acid and perfluorooctanesulfonic acid), Mechanistic Evidence Subgroup (member)
- NCTR SSRP (committee member)
- OECD Expert Group in Skin Absorption
- South Central Chapter of SOT (President, Graduate Student Poster Presentation Award Selection Judge, Undergraduate Student Travel Award Selection Judge)

## Presentations

- SOT 2023 Annual Meeting (17 presentations)
- South-Central Chapter of SOT 2023 Annual Meeting (2 presentations)
- Fall 2023 Tobacco Regulatory Science Meeting (3 presentations)
- FDA Science Forum (3 presentations)
- 9th Annual AR-BIC
- 114th Annual Meeting of the American Association for Cancer Research
- American College of Clinical Pharmacology Annual Conference
- Arkansas Water Conference


*DBT researchers attended Society of Toxicology Annual Meeting in March 2023*

- Chem-Academy Annual Conference on Endocrine Disruptors
- Gordon Research Conference on Barrier Function of Mammalian Skin
- National Capital Area Chapter-SOT and CFSAN Joint Fall 2023 Symposium: Applied Toxicology and Risk Assessment
- Organization for the Study of Sex Differences Annual Meeting

## Scientific Journal Editors and Grant Reviewers

- *Journal of Environmental Science and Health, Part C: Toxicology and Carcinogenesis* (Editor-in-Chief and Associate Editor)
- "Pharmacology, Toxicology, Pharmaceutical Sciences" section of *Data in Brief* (Section Editor)
- *Toxicogenomics* (Associate Editor)
- *Food and Chemical Toxicology* and *Toxicology Letters* (Editorial Board Member)
- FDA Office of the Chief Scientist Challenge FY2024 Intramural Grants (Reviewer)

## Other Outreach

- Office of Equal Employment Opportunity, Diversity & Inclusion Department of Health and Human Services: "Health Disparities in African-American and Minority Communities and Available Resources" (panelist)
- Organized NCTR Summer "Lunch and Learn" Lecture Series for 2023 ORISE SSRP
- Pharmacokinetics course at University of North Texas Health Science Center: "Digoxin" (guest lecturer)
- Pharmacokinetics course at University of North Texas Health Science Center: "Obesity" (guest lecturer)
- UAMS Systems Pharmacology and Toxicology (SPaT) T23 Program (invited training faculty staff member)
- UAMS SPaT Workshop: "Radiation Impacts on Toxicity of Cobalt-Chromium Implant Debris" (presenter)
- UAMS Systems therapeutics course: "The role of quantitative modeling in pharmacology and toxicology" (invited lecturer)

# Division of Bioinformatics & Biostatistics

***NCTR's Division of Bioinformatics and Biostatistics (DBB) develops integrated bioinformatics and biostatistics capabilities to address increasing need in areas such as biomarker development, drug safety, drug repositioning, precision medicine, artificial intelligence, rare diseases, endocrine disruptors, and risk assessment.***

## 2023 Select Accomplishments

- Made significant progress in several focused areas, including the opioid crisis, CBD, endocrine disruptors, drug safety, COVID-19, toxicogenomics, and precision medicine, and specifically, in AI/Machine Learning (ML).
- Developed **DICTrank** (Drug-Induced Cardiotoxicity Rank), the largest reference list of 1,318 human drugs ranked by risk of drug-induced cardiotoxicity using FDA labeling, which facilitates the development of NAMs (*Drug Discov Today*).
- Developed **AnimalGAN**, a Generative Adversarial Networks (GAN) model that simulates animal studies to reduce animal use in preclinical studies for drug development (*Nature Comm*).
- Led five projects that were newly funded by FDA intramural grants on the following topics: **AI bias** funded by OCS, **drug safety in women's health** by OWH, **COVID-19 and its variants** by the Medical Countermeasures Initiative, and **real-world data for minority health** by Office of Minority Health and Health Equity.
- Published approximately 38 manuscripts, some in well-respected journals such as *Nature Biotechnology*, *Nature Communications*, and *Genome Biology*.
- Awarded the **One NCTR Challenge Coin**—Dr. Dongying Li—for her outstanding contributions to NCTR's efforts at the 2023 AR-BIC and the 2023 SOT Conference. Dr. Li's exceptional dedication and teamwork went "above and beyond" to advance NCTR's mission, showcase NCTR's capabilities, and promote NCTR for regional, national, and international collaborations.

***Division Director — Weida Tong, Ph.D.***

**Bioinformatics**
***Branch Chief — Huixiao Hong, Ph.D.***

Constructs knowledge bases to provide a data-driven decision-making environment for enhanced safety evaluation and precision medicine

**Biostatistics**
***Branch Chief — Dong Wang, Ph.D.***

Conducts research of statistical methods to analyze toxicological and molecular data as well as data-mining techniques for pattern identification and signal detection

**Scientific Computing**
***Branch Chief — Edward Bearden***

Provides IT support to all of NCTR

**Review-to-Research and Return (R2R)**
***Branch Chief — Joshua Xu, Ph.D.***

Translates division research for regulatory application

## By the Numbers

| | |
|---|---|
| 38 | papers published |
| 35 | platform presentations delivered |
| 26 | posters presented |
| 26 | scientific conferences attended |
| 7 | concept papers submitted |
| 6 | projects completed/closed |

***For more information on NCTR Bioinformatics Tools, visit www.fda.gov/NCTRBioinformatics.***

# Outreach

In 2023, DBB scientists contributed to or participated in the following outreach events:

- 9th AR-BIC Annual Conference — Scientific Program Committee (chair)
- 13th Annual Global Summit on Regulatory Science (chair)
- Cheminformatics Resources of U.S. Governmental Organizations — FAIR-ifying and Sharing Chemical-Related Data session (chair); "Machine Learning Models for Rat Multigeneration Reproductive Toxicity Prediction" (presentation)
- FDA 11th Annual Scientific Computing Days (three posters presented and one breakout session hosted)
- Institute of Electrical and Electronical Engineers-USA Innovation, Workforce, and Research Conference — The conference showcased innovative research conducted by various divisions at NCTR, adding a valuable dimension to the event. The exhibit attracted numerous participants who were interested in the types of research and job opportunities available at NCTR (three DBB staff represented NCTR).


***Three DBB researchers attended the Institute of Electrical and Electronic Engineers-USA Innovation, Workforce, and Research Conference in Little Rock, AR, September 2023***

- Large Language Model (LLM) workshop hosted by Swissmedic and instrumental in establishing the interagency LLMs Workforce (DBB staff led this first ever workshop)
- "Making Sense of Electronic Health Record (EHR) Race and Ethnicity Data Challenge" — The Biostat Team provided important insight on how to interpret and improve the collection of race/ethnicity data in electronic health records, and was named as one of the top performers in precisionFDA
- SOT 62nd Annual Meeting and ToxExpo (DBB staff played a pivotal role in the ToxExpo preparations and event)

## SOT Poster Sessions

- "AnimalGAN: A Generative AI Alternative to Animal Clinical Pathology Testing" (X. Chen)
- "A Systematic Analysis and Data Mining of Opioid-Related Adverse Events Submitted to the FAERS Database" (H. Le)
- "Assessment of Modified Sandwich Estimator for Generalized Estimating Equations with Application to Opioid Poisoning in MIMIC-IV ICU Patients" (P. Rogers)
- "RxNorm for Drug Name Normalization: A Case Study of Prescription Opioids in the US FDA Adverse Events Reporting System" (W. Zou)
- "Using Language Model to Facilitate COVID-19-Associated Neurological Disorder Literature Analysis: A BERTox Research" (L. Wu)
- "Development of Random Forest Model for Predicting SARS-CoV-2 Main Protease Binders as Potential Candidates for Repurposing to COVID-19 Treatment" (L. Xu)
- "Opioid Agonist/Antagonist Database (OADB): A Database to Facilitate Opioid Drug Development" (F. Dong)
- "Machine Learning Models for Rat Multigeneration Reproductive Toxicity Prediction" (J. Liu)
- "Machine Learning for Predicting Risk of Drug-Induced Autoimmune Diseases by Structural Alerts and Daily Dose: (M. Chen)
- "Obtain Drug Safety Rankings through Meta-analysis of Clinical Trial Data Using Penalized Bayesian Model" (D. Wang)
- "Deep Learning-Based Genotype Imputation for Enhancing Toxicogenomic Data" (M. Song)
- "Statistical Methods for Exploring Spontaneous Adverse Event Reporting Databases for Drug-Host Factor Interactions" (Z. Lu)
- "Development of a Large List of Drugs for the Study of Nephrotoxicity in Drug Discovery" (S. Connor)
- "Random Forest Model for Predicting μ Opioid Receptor Binding Activity for Assisting Development of Opioid Drugs" (Z. Li)
- "DeepAmes: Deep Learning-Powered Ames Test Prediction Using Model-Level Representation" (T. Li)
- "Informing Selection of Drugs for COVID-19 Treatment through Analysis of Adverse Events" (W. Guo)
- "hnRNP-Q and hnRNP-L Influence Drug Metabolism and Toxicity by Regulating mRNA Processing of Drug Metabolizing Enzymes and Nuclear Receptors in HepaRG Cells" (D. Li)
- "hnRMP-Q and hnRMP-L Influence Drug Metabolism and Toxicity by Regulating mRNA Processing of Drug Metabolizing Enzymes and Nuclear Receptors in HepaRG Cells" (D. Li)

# Division of Genetic & Molecular Toxicology

***The mission of NCTR's Division of Genetic & Molecular Toxicology (DGMT) is to improve public health by providing FDA with the expertise, tools, and approaches necessary for the comprehensive assessment of genetic risk.***

**DGMT Leadership**

*Division Director – Robert Heflich, Ph.D.*
*Deputy Director – Mugimane Manjanatha, Ph.D.*

## In 2023, DGMT Scientists

- Collaborated with other FDA product Centers/Offices on 16 projects.
- Gave 16 poster and 9 oral presentations at the annual **Environmental Mutagenesis and Genomics Society** and **SOT** conferences.
- Gave four presentations at the UAMS **Systems Pharmacology and Toxicology Workshop (SPaT)**.
- Gave oral presentations at FDA Grand Rounds, FDA Innovation and Quality Microphysiological Systems (IQ MPS) Affiliate, Office of New Drugs, and the Genetic Toxicology subcommittee of the CDER Pharmacology-Toxicology Coordinating Committee.
- Invited to participate in the OECD Expert Group on Genetic Toxicology, and the HESI/GTTC on advancement of genetic toxicology; submitted a proposal to the OECD to revise existing OECD genetic toxicology Test Guidelines.
- Participated in 15 FDA working groups, committees, and subcommittees and 36 external working groups including the Interagency Coordinating Committee on the Validation of Alternative Methods.
- Presented talks and posters at the **FDA Science Forum** and chaired/moderated two sessions attracting over 250 attendees across FDA.
- Published 18 **scientific reports** and have 7 manuscripts in press.
- Received 2 **FDA group awards**, and 8 **NCTR awards** (including the NCTR Director's Award), and 7 special act/service awards.
- Received seven competitive **intramural-funding awards** (e.g., CDER Office of New Drugs, CDER Office of Pharmaceutical Quality, CTP, and NTP).

***Division Goals:***

- Responding to Agency needs for genetic toxicology expertise and chemical-specific data
- Maintaining DGMT's tradition of leadership in regulatory genetic toxicology assay development and validation
- Developing better methods for carcinogenicity testing and translation of rodent studies to human cancer risk
- Developing advanced in vitro toxicological models that incorporate genotoxicity endpoints

## By the Numbers

| | |
|---|---|
| 36 | external working groups |
| 18 | scientific reports published |
| 17 | FDA/NCTR awards |
| 16 | collaborations with FDA centers |
| 15 | FDA working groups |
| 7 | competitive intramural-funding awards |

## 2023 Select Accomplishments

***Quantification of Genomic Damage by Next Generation Sequencing of Whole Genomes***

DGMT scientists quantified in vivo genomic damage by whole genome clone analysis and high-fidelity (HiFi) ecNGS. HiFi ecNGS was used to evaluate ultrarare off-target mutations in genome-edited cell populations. These ultrarare off-target mutations could lead to cancer and their analysis provides important information to FDA for regulation of therapies based on gene editing. This work was described in *Environ Mol Mutagen*.

# Accomplishments (Cont.)

### *Evaluation of Nitrosamine Genotoxicity Using In Vitro and In Vivo Models*

*N*-Nitrosamine drug impurities are a major concern for FDA, especially nitrosamine impurities formed by the drug substance itself, termed *N*-nitrosamine drug substance-related impurities or NDSRIs. Impurities can form at any time during the drug life cycle, for example, as by-products of synthesis, during storage, and as NDSRIs generated in the treated patient. *N*-Nitrosamine impurities that are likely to increase the risk of cancer are identified using mutation assays; *N*-nitrosamines that are mutagenic are assumed to be carcinogenic and are controlled at very low levels in drugs. Therefore, it is important for FDA to develop test models that can identify mutagenic *N*-nitrosamines. DGMT scientists have collaborated with the CDER Nitrosamine Drug Impurity Task Force to evaluate the mutagenicity and genotoxicity of a series of small-molecule *N*-nitrosamines and NDSRIs using in vitro bacterial and human cell mutation assays. Also, eight different *N*-nitrosamines were tested for their genotoxicity using 2-dimensional (2D) and 3-dimensional (3D) human hepatic (HepaRG) cell models. Finally, different *N*-nitrosamines are being evaluated for their mutagenicity in transgenic rodents. The objective of these studies is to develop screening and follow-up assays that determine the cancer risk of *N*-nitrosamine drug impurities with a high degree of confidence. The following publications describe the results from these studies: *Regul Toxicol Pharm* and *Arch Toxicol*.

# Collaborations and Outreach

- FDA's CDER, along with NCTR's DBT and DGMT, used CarcSeq to detect DNA sequence alterations caused by the non-genotoxic carcinogen, lorcaserin, in treated rats. CarcSeq is an ecNGS technique developed in house to quantify expansions of Cancer Driver gene Mutations (CDMs).
- DGMT, HESI/GTTC, University of Ottawa, Health Canada, and Twin Strand Biosciences advanced nonclinical genotoxicity and carcinogenicity testing by using ecNGS to evaluate the mutations induced in mice treated with a mutagenic carcinogen. This multi-lab study analyzed mutations in multiple tissues, including CDMs by the CarcSeq technique (*Nat Rev Drug Discov*).
- DGMT and FDA's CVM adapted a high-throughput micronucleus (MN) assay to both 2D and 3D (spheroid) human hepatic HepaRG cultures for in vitro genotoxicity testing. They used the flow-cytometry-based MN assay for genotoxicity evaluation of >30 chemicals. Positive responses in the MN assay were quantified using Benchmark Concentration (BMC) potency ranking (*Arch Toxicol*).
- DGMT and CDER Nitrosamine Drug Impurity Task Force enhanced the bacterial Ames assay for detecting the mutagenicity of *N*-nitrosamine drug impurities and develop follow-up in vitro mammalian cell assays for confirming Ames assay results. The findings from the project are discussed at monthly meetings with the CDER *N*-Nitrosamine Drug Impurity Task Force and have contributed to three guidance documents issued by CDER and other regulatory agencies on how best to evaluate the mutagenicity of *N*-nitrosamine drug impurities. Also tested several *N*-nitrosamines as part of a multi-lab project with other research organizations and industry stakeholders.
- DGMT and CTP scientists validated Vitrocell exposure systems to investigate the in vitro toxicity of aerosols from electronic nicotine delivery systems and whole tobacco smoke from conventional cigarettes through exposures at the air-liquid interface of human airway-tissue models.
- DGMT researchers and UAMS clinicians evaluated mutation in the *PIG-A* gene of blood cells from cancer patients who were treated with antineoplastic drugs.
- DGMT scientists collaborated with scientists from academia, industry, and other regulatory agencies in international consensus-building efforts to improve the science of genetic toxicology by publishing white papers on:
  - » the use of historical control data for evaluating genetic toxicology assay responses (*Environ Mol Mutagen*)
  - » using in vitro genotoxicity assays for tobacco product toxicity assessments (*Altern Lab Anim*)
  - » conducting the Comet assay (*Nat Protoc*)
  - » performing in vitro to in vivo extrapolation with genetic toxicology data (*Environ Mol Mutagen*)
  - » the promise of ecNGS for revolutionizing regulatory mutation assessments (*Mutat Res Rev Mutat Res*)
  - » using the in vivo *Pig-a* assay for mutational hazard assessment (*Environ Mol Mutagen*)

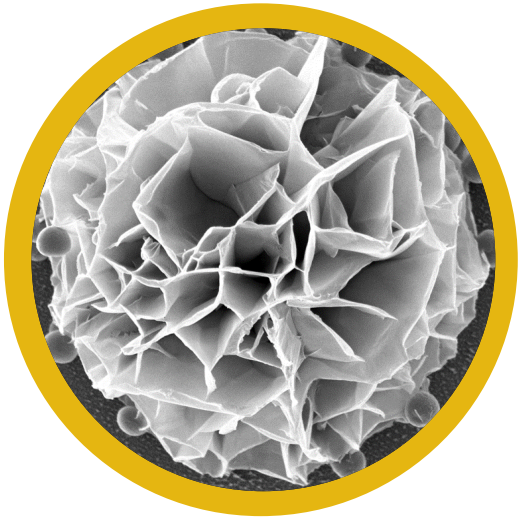
# Division of Microbiology

***NCTR's Division of Microbiology (DM) serves a multipurpose function including evaluating the impact of antimicrobial agents, food contaminants, food additives, nanomaterials, and FDA-regulated products on the microbiome; developing methods to detect and characterize microbial contaminants; determining antimicrobial resistance and virulence mechanisms; conducting research to aid FDA in the areas of women's health, tobacco products, and nanotechnology; and improving risk assessments.***

**DM Leadership**
*Division Director – Steven L. Foley, Ph.D.*

## In 2023, DM Scientists

- Received **NCTR Director's Award** for outstanding research efforts in support of CDER's compounded drug safety efforts.
- Received **NCTR Outstanding Service Award** for initiative and perseverance to bring new approaches and techniques to support Division multidisciplinary and technology-driven research projects.
- Presented at **FDA Grand Rounds**, "The Plasmid Puzzle: Finding Solutions in *Salmonella*."
- Served on planning committees for **AR-BIC** conference, **FDA Science Forum**, **FDA Microbiome Day**, and **FDA Omics Day** series.
- Organized a monthly seminar speaker series to feature prominent microbiologists who present virtually to groups ranging from 30-45 attendees.
- Collaborated with **NTP** to assess the role that microbiome may play in the toxicity of xenobiotics.
- Collaborated with **CFSAN** to generate significant data on the microbial contamination of tattoo inks. These results have led to multiple publications and aided in understanding the potential risks of tattoo inks.
- Collaborated with **CDER** to address data gaps in the safety of compounded pharmaceuticals.
- Collaborated with **CVM** characterizing antimicrobial resistance and pathogenicity in foodborne and zoonotic pathogens.



***Electron Microscopy Image:***
***Following a 10-minute exposure of* Staphylococcus aureus *HAR12 to a nanostructured copper surface, a distinctive flower-like structure formed, and the cells adhered to this unique configuration (Courtesy: Dr. Kidon Sung)***

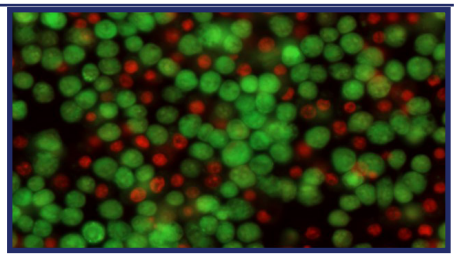
## By the Numbers

| | |
|---|---|
| 30 | posters presented |
| 20 | platform presentations delivered |
| 20 | papers published |
| 14 | scientific conferences attended |
| 6 | projects completed/closed |
| 5 | concept papers submitted |

## Collaborations

- 11 collaborations with other NCTR divisions
- 15 collaborations with other FDA centers
- 5 collaborations with outside entities (non-FDA)

# 2023 Select Accomplishments



*In this image, the green cells are live macrophages (immune cells) and the red cells are macrophages that have been killed by virulent* Salmonella *strains (Courtesy: Dr. Kuppan Gokulan)*

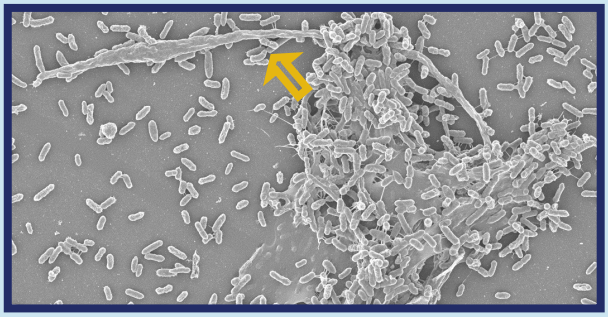
### *Developing a Plasmid Analyses Toolbox*

NCTR collaborated with CVM scientists to develop tools and approaches to cure bacterial plasmids—genetic structures outside of the bacteria's chromosome that often carry genes encoding for AMR and/or virulence traits—and specifically remove plasmid genes to identify their functions related to virulence and AMR.

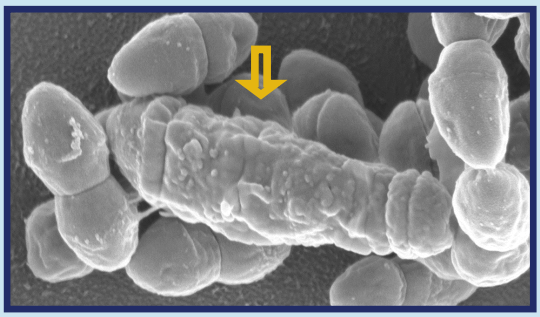
These efforts will help researchers better understand the factors that increase the ability of resistance plasmids to be shared among bacteria spreading AMR. Recent publications describing this work are available in the journals, *BMC Genomics*, *Front Microbiol*, and *Microbiology Spectrum*.

### *Using Biofilm Models to Study AMR*

Biofilm-associated infections associated with implanted medical devices is a major challenge and public health concern. During treatment, bacterial cells in biofilms may be exposed to sublethal concentrations of the antimicrobial agents which can drive antimicrobial resistance development. These studies demonstrate that global protein expression differences within biofilms following antibiotic pressure may improve our understanding of the mechanisms of antibiotic resistance in biofilms. A recent publication describing this work is available in the journal, *Pathogens*.



*This image illustrates the pivotal role of uniquely elongated* Proteus mirabilis *ATCC 7002 cells in the process of biofilm formation (Courtesy: Dr. Kidon Sung)*



*This SEM image illustrates the significant contribution of the unusually enlarged cells of* Enterococcus faecalis *ATCC 29212 in the process of biofilm formation (Courtesy: Dr. Kidon Sung)*

### *Surveying Microbial Contaminants in Commercial Tattoo Inks and Other Related Products*

Tattooing and the use of permanent makeup inks have dramatically increased over the last decade. It is estimated that between 20-30% of the U.S. population have at least one tattoo. The process of tattooing involves the injection of different inks into the skin, thereby breaking the epithelial layer that serves as a protection from infection. If inks used for tattooing contain microorganisms, there is the chance for infections to develop. This research found that microbial contamination in commercial tattoo inks and related products is not rare and might be potential sources of human infections, presenting a significant public health concern. With the growing tattoo industry and the global supply chains for tattoo inks, a deep understanding of the microbial contamination in these products is important. A recent publication describing this work is available in the journals, *Front Public Health*.

## Completed Projects

- An assessment of the interactions of nanoscale ($TiO_2$ and ZnO) materials used in sunscreens on the skin microbiome
- Studies on the intrinsic structural multidrug efflux pump mechanisms in antimicrobial resistant *Salmonella enterica* and their role in antimicrobial resistance
- Anaerobic bacterial detection in tattoo inks and other related products

## Ongoing Projects

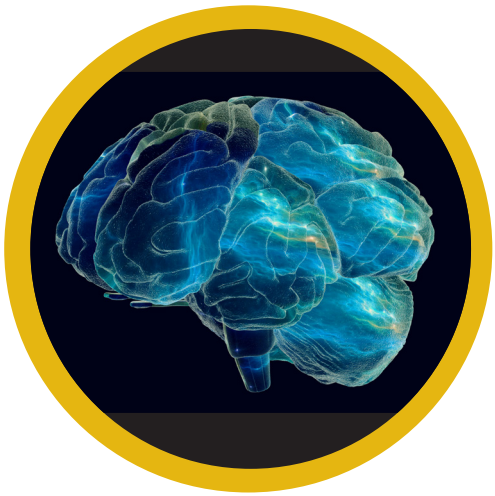
- Standardized methods for sporicidal efficacy assessment and building up an efficacy database of sporicidal products
- Safety assessment of nanocrystal drug to determine effects on the gastrointestinal tract microbiome and functions
- Recombinant coronavirus spike proteins to generate reagents, study cell interactions, and antibody-dependent enhancement
- Evaluation of antimicrobial, antibiofilm and cytotoxicity activity of nanoparticles, and nanostructured surfaces

# Division of Neurotoxicology

***The mission of NCTR's Division of Neurotoxicology (DNT) is to identify/quantify neurotoxicity related to FDA-regulated products, develop and qualify quantitative biomarkers of neurotoxicity, and identify biological pathways associated with the expression of neurotoxicity to improve risk assessments and new approaches for diagnosis, as well as supporting the evolving needs of FDA product centers.***

## DNT Leadership

***Division Director – John Talpos, Ph.D.***



## By the Numbers

| | |
|---|---|
| 41 | active protocols |
| 11 | posters presented |
| 8 | papers published |
| 6 | projects completed/closed |
| 3 | scientific conferences |

## 2023 Select Accomplishments

### *DNT Research Presented at Society of Toxicology Annual Meeting*

- Division efforts to identify minimally invasive markers for central nervous system (CNS) toxicity led to development of an effective myelin-damage model. This project is in collaboration with an international consortium of leading scientists that represent regulatory bodies such as CDER, other partner agencies like CDC and EPA, and various industry and pharmaceutical partners. Initial data from this project was presented by Division staff at the 2023 SOT annual meeting where sensitivity of $T_2$ Magnetic Resonance Imaging (MRI) was demonstrated in the early detection of grey matter damage in CNS in an oral rat model of cuprizone-induced neurotoxicity.

- Results from a study evaluating the mechanism of ketamine-induced neurotoxicity was also presented at the 2023 SOT annual meeting. Division staff presented results showing a potential sex and aged dependent effect of ketamine on the central nervous system. Young rats (21, 30, 35 days old) or adult rats (90 days old) were exposed to a single high dose of ketamine. Interestingly, neurotoxicity was only observed in female animals exposed to the highest dose of ketamine. This finding was a surprise since younger rats had higher blood levels of ketamine. However, adult female animals had significantly higher levels of norketamine, a primary metabolite of ketamine. These data suggest that adolescent rats are not at increased risk for ketamine-induced neurotoxicity and highlight the potential impact of norketamine on ketamine-induced neurotoxicity.

### *Advancing the Use of $T_2$ MRI to Assess Neurotoxicity*

For over a decade, DNT researchers have explored how $T_2$ MRI can be used to study neurotoxicity. This noninvasive method allows real time assessment of toxicity, meaning multiple assessments can occur in the same animal. This approach may be faster and require fewer animals than traditional safety assessments.

# Accomplishments (Cont.)

## Awards

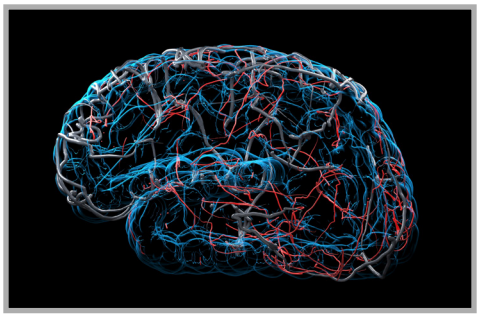
Several Division staff received awards in 2023 for varying degrees of services in accomplishing the mission and goals of NCTR. A highlight amongst these was the **NCTR Director's Award** for outstanding dedication to training and motivating the next generation of scientists, awarded to Dr. Sumit Sarkar. As part of **NCTR's SSRP**, Dr. Sarkar has mentored numerous undergraduate and high school students in neuroscience and neurotoxicology research, many who continued a career in science at prestigious graduate and medicine programs nationwide. Moreover, Dr. Sarkar regularly instructs NCTR staff of all levels in advanced neurohistological methods. Dr. Sarkar also works to promote science in the general community by regularly judging at science fairs throughout the state.

## Funding

- Secured further funding from PHCE to study the long-term effects of neonatal opioid withdrawal syndrome in rats, as well as the interactions between opioids and cannabinoids on in vitro models of human brain development.
- Collaborated with NCTR's DM on a project designed to study the impact of diet and gender on the development of Parkinson's disease. The project has been short-listed for funding from the OWH.

## Presentations

- Gave 4 lectures as part of the FDA-wide **Practical Neurotoxicology Course organized by CDER's Neurotoxicity Assessment Subcommittee**. Presentations highlighted ongoing Division research on complex animal behavior analysis, use of zebrafish as an alternate model for screening of neurotoxicity, and current advances in minimally invasive biomarkers of CNS toxicity.
- Participated in the 2-day public workshop, **State of the Science on Assessing Developmental Neurotoxicity Using NAMs** at the Joint Institute for Food Safety and Applied Nutrition. Presentations included how NAMs are being used to enhance data gained from traditional animal models in regulatory settings, and what capabilities would be lost in transition to an in vitro-based assessment approach.



# Collaborations

- DNT and FDA's CFSAN researchers showed that arsenic exposure to zebrafish eggs and larvae induced developmental neurotoxicity (*J Appl Toxicol*). While it is likely that multiple pathways are involved in arsenic toxicity, additional research is ongoing exploring how the Sonic Hedgehog (SHH) pathway may result in an overproduction of motor neurons in the zebrafish (*Neurosci Lett*). Additional work is aimed at developing an OECD adverse outcome pathway that can document how alterations to the SHH pathway may result in neurodevelopmental disorders.
- DNT continues its longstanding collaboration with The Icahn School of Medicine at Mount Sinai on evaluating neurobehavioral effects on heavy metal exposure in children. This collaboration, in conjunction with Mexico's National Institute of Perinatology, has resulted in multiple publications linking heavy metal exposures to changes in cognitive performance (*Environ Res*).
- DNT and HESI continue to evaluate the development of minimally invasive biomarkers of neurotoxicity in preclinical models. A goal of this project is to link changes in MRI imaging with potential blood-born biomarkers for neurotoxicity.

# Completed Projects

- Addendum Assessment of the Gaseous Anesthetic, Desflurane, in the Developing Nonhuman Primate
- Analysis of Sex Differences in Amyloid Beta Transporters of the Cerebral Vasculature in Alzheimer's Disease
- Evaluation of Neuronal Loss and Neuroinflammation in Diabetic Ketoacidosis (DKA) of Type1 Young Diabetic Patient Population
- Obtaining Neural Stem Cells from Monkey Fetuses to Study Anesthetic-Induced Developmental Neurotoxicity
- Piloting the Use of 3-Dimensional Accelerometers to Measure Hyper-Locomotion in the Nonhuman Primate
- Preliminary MRI and Histopathological Evaluation of Gadolinium Deposition in the Rat Brain
- The Effects of Withdrawal from Chronic Methylphenidate Administration on Cognition, Markers of Brain Function, and Sensitivity to Drugs of Abuse

# Division of Systems Biology

**Division Leadership**
*Division Director – Laura Schnackenberg, Ph.D.*
*Deputy Director – Jessica Hawes Oliphant, Ph.D.*
*OMIC Branch Chief – Richard Beger, Ph.D.*
*IST Branch Chief – Laura Schnackenberg, Ph.D.*

***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 Accomplishments

As part of the annual NCTR SAB meeting, DSB was highlighted with an in-depth SAB Subcommittee review. As noted by the review, "investigators within the DSB presented project reviews addressing important questions and unmet needs" in the scientific areas of Clinical/Translational Omics Biomarkers, Predictive Toxicology, Therapeutic Safety & Product Center Support, and Response to Health Threats/Emergencies. Results from DSB studies were shared publicly in 12 open-access literature publications and at a variety of internal FDA, national, and international scientific conferences. 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 NAMs in predictive toxicology, vaccines, cannabinoids, and biomarker research. Approximately 25% of DSB research projects were successful at recruiting competitive project funding awards in 2023. DSB staff also served the local and FDA community on a variety of FDA and NCTR working groups, as well as co-chairing or serving on committees for numerous external scientific conferences and organizations.


*Dr. Qiang Shi represented NCTR and DSB at American Possibilities: A White House Demo Day*

### *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 clinical informed prediction of anthracycline-induced cardiotoxicity 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 MPS, 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 recently at the ACT 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 SOT conference regarding "Moving Stem Cell-Derived New Approach Methods toward Regulatory Acceptance."
- Organized an FDA study with investigators at multiple 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.

# Accomplishments (Cont.)

***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.
- Conducted lipidomic, metabolomic, and proteomic research to support evaluating pathogen-reduced platelet approaches for CBER collaborators, 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 (***page 15***)
- 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.

# By the Numbers

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

# In 2023, DSB Scientists

- Assisted in organizing **FDA's 2022 Multi-Component Biomarker Workshop** and wrote the associated white paper that was published in 2023 in *Biomark Med*.
- Gave approximately **65 oral presentations** (at least 47 FDA internal and 18 external) and presented **37 posters** (17 FDA internal and at least 20 at external scientific conferences).
- Led the **Montelukast Working Group**, in coordination with CDER 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.
- Participated in approximately **28 FDA working groups** and committees/subcommittees, and **17 external working groups**.
- 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 CFSAN, reviewing preclinical studies for the potential cardiovascular risk of erythritol.
- Represented NCTR and presented a talk on regulatory science research supporting rare diseases at the **FDA Rare Diseases Day** public meeting.
- 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.
- Served as judges for local high school science fair.
- Served as mentors in NCTR's SSRP and FDA's Office of Data, Analytics, and Research Applied Learning Track Program.
- Served on the review committee for grants/scholarships for American Indian Science and Engineering Society A.T. Anderson Scholarship and Empowering Scholarship Account in 2023.

# Collaborations

DSB leadership continues to encourage collaboration with subject matter experts internal to FDA and NCTR and externally. Of the 66 active research projects during 2023, all were collaborative, totaling 235 individual collaborators and 506 individual collaborations, reflecting the overlap of multiple individuals collaborating on numerous DSB projects. Most DSB projects (88%) involve collaborators at other FDA Centers or Offices, consistent with the Division's mission to address regulatory research needs. Slightly over one-third of DSB projects (36%) also include collaborators across 36 different external academic institutions or scientific consortia, 11% include collaborating experts at 7 other government agencies, and another 11% have collaborators at 13 different industry groups.

# Office of Scientific Coordination

***NCTR's Office of Scientific Coordination (OSC) provides the professional support necessary to conduct toxicology studies in support of FDA and NCTR's research mission. This support is provided by the following support groups: Analytical Chemistry, Experimental Support, Microbiology Surveillance Laboratory, Nanotechnology, Statistics, Veterinary Services, Animal Care Contract, Pathology Services Contract, and Equipment Maintenance and Repair Contract.***

### *Analytical Chemistry*

Analytical Chemistry research and support are conducted using trained staff and state-of-the-art instrumentation for processing of a wide range of samples. Test articles and their metabolites are assayed in blood, tissues, or urine to provide measures of exposure and, for genotoxic compounds, DNA adducts are measured. The high quality of studies at NCTR is ensured by 1) verification of test-article identity and purity, 2) formulation of dosing solutions, 3) certification of concentration and stability of test articles in dosing solutions and vehicles, and 4) routine surveillance of animal study materials (bedding, water, and diet).

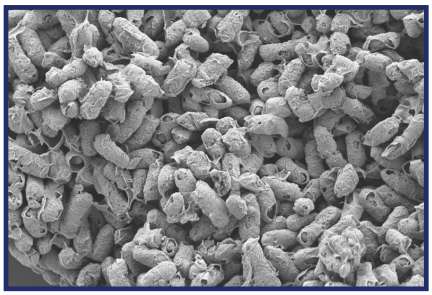
### *Experimental Support*

Experimental Support staff provide computer-based support for animal studies. The staff reviews study protocols and works with research and support staff to enter study parameters in the animal data collection system, reviews data, and generates reports at the conclusion of studies.

### *Microbiology Surveillance*

The Microbiology Surveillance Laboratory staff ensures research animals, environments, food, bedding, and test articles are free from opportunistic pathogens and supports personnel health by routinely monitoring the microbiological quality of NCTR drinking water and environmental samples. They provide accurate and timely identification and characterization of microbes using advanced technologies including biochemical metabolism, MALDI-TOF mass spectrometry, and NGS. The laboratory staff also supports other microbiology-related research studies from the research divisions.

### *Nanotechnology Core Facility*



***Field Emission Scanning Electron Microscopy (FE-SEM) images of* Salmonella inverness *bacteria showing holes in the cell wall after treatment with distilled water for 182 days. (Courtesy: Dr. Angel Paredes with Anna Williams and Drs. Pierre Alusta and Dan Buzatu)***

**Office Leadership**

***Associate Director – Bradley Schnackenberg, Ph.D.***
***Analytical Chemistry – Matthew Bryant, Ph.D.***
***Microbiology Surveillance – Sung Guk Kim, Ph.D.***
***Veterinary Services – Pamela Mack, DVM, MS, DACLAM***
***NanoCore – Anil Patri, Ph.D***

The NCTR/ORA NanoCore supports collaborative nanotechnology research within FDA and research between FDA and other government agencies and universities. This facility is well-equipped with advanced analytical equipment for nanomaterial assessment. Apart from these, laboratories are equipped for in vitro and in vivo biological studies. NanoCore research provides information on nanomaterial characterization and the safety of products containing nanomaterials in FDA-regulated products. This research data is also used in staff and reviewer training and in establishing standards for use by stakeholders developing nanotechnology products.

### *Statistics*

The Statistical Support staff provides traditional statistical support for the various toxicity studies conducted at NCTR. The services provided include statistical consultation during protocol development, statistical randomization, statistical analysis, and statistical reporting.

### *Veterinary Services*

Veterinary Services staff ensure the health and welfare of all animals used in research. The veterinarians participate in the review and monitoring of animal use through the Institutional Animal Care and Use Committee (IACUC). They advise scientists regarding study design, performing surgery on animals, and monitoring the overall health of the animal program. Veterinary Services also includes the Microbiology Surveillance support staff. This facility has been Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC) accredited since 1977.

#### Animal Care Contract

NCTR maintains an on-site contract with trained and proficient staff to provide study support including husbandry, environmental enrichment of all animals, administration of test articles, sample collection, and data collection. The contractor works with the veterinary staff and the IACUC to ensure the health and welfare of the animals.

**Pathology Services Contract**

NCTR maintains an on-site pathology contract for veterinary pathology and histopathology services. The contractor maintains a staff of two full-time veterinary pathologists and a highly trained staff that provide NCTR with services including: clinical pathology, histopathology slide preparation, rigorous pathology examination, and complete histopathology and pathology reports for each study.

**Equipment Maintenance and Repair Contract**

NCTR maintains a contract for equipment maintenance and repair that supports the routine preventative maintenance and calibration of equipment, manufacture of minor equipment to support customized research needs, and repair of equipment that is not on a service agreement with the manufacturer.

# Outreach Activities

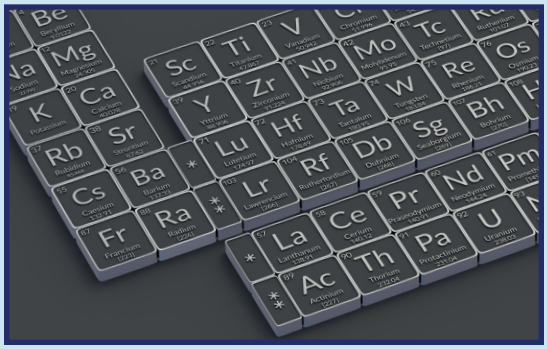
In 2023, OSC staff contributed to or participated in the following outreach events:

- American College of Laboratory Animal Medicine Information Technology Management committee
- American Society of Laboratory Animal Practitioners Community Outreach Committee
- Organized 2023 NanoDay Symposium: Continuous Manufacturing of Nanomaterials," by CDER-Small Business and Industry Assistance
- Organized Nanotechnology Workshop at GSRS23, Parma, Italy

# 2023 Select OSC Accomplishments

## Chemistry

- Developed high-performance liquid chromatography-mass spectrometry (HPLC-MS) methods for the analysis of several opioids (methadone, morphine and buprenorphine) to verify the concentration of oral dose formulations in a rat study. Analyzed rat plasma samples from these studies to determine the achieved in vivo exposures.
- Added the preparation of dose formulations to the Analytical Chemistry Group's support functions.
- Developed a gas chromatography with flame-ionization detection method to evaluate the purity of tritiated 1,4-dioxane test article and provided an evaluation of several lots of material provided by the manufacturer.
- Investigated possible formulations to be used in a high-dose studies of acetaminophen, glyburide, and metformin in rats. Conducted dose certifications of these suspensions prior to their use in these animal studies.
- Upgraded instrumentation with the purchase of two new ultra-performance liquid chromatography-Tandem mass spectrometer systems which will be used in bioanalytical projects supporting multiple studies and FDA Centers. Also replaced two obsolete HPLC systems with a new HPLC system that will be used to conduct dose formulation certification studies.
- Conducted analysis of nicotine, propylene glycol, and vegetable glycerin in filters and liquid exposure inserts from a conventional cigarette smoking robot to ensure proper validation of target exposures for future in vitro studies.



## Microbiology Surveillance

In 2023, the microbiology surveillance unit developed two new diagnostic methods for use within the unit:

- **Sequencing-based Diagnostic Methods** — A new 16s rRNA sequence-based method was introduced and is currently extending its services for more organisms
- **Endotoxin assay** — Optimization is currently underway and the test will be available to NCTR investigators in 2024

## Veterinary Services

- Supported IACUC with administrative functions and active participation of 2 voting members.
- Maintained high standards of animal care including compliance with the Animal Welfare Act and regulations, Public Health Service regulations, and AAALAC standards.
- Assisted in the implementation of three new animal models to answer critical questions with agents of concern to the FDA.

# Office of Management

**Office Leadership**

*Associate Director for Operations & Office of Management – Denny Skiles*
*Planning & Resource Management – Barry W. Downing & Richard Keach*
*Executive Programs & Services – Dawn Johnson*
*Communications Branch – Tonya Vyas*

***NCTR's Office of Management (OM) is integral to NCTR operations, and its diverse portfolio represents enterprise-level efforts in communications, protocol processing, property, and space management. OM contributes to the efficient and economic handling of NCTR business-specific operations including human capital, finance, acquisitions, contract management, operational planning, and management of NCTR's external funding agreements.***

## *Planning and Resource Management*

Planning and Resource Management (PRM) staff provide a suite of business support services, operations, and tools with the following functional responsibilities:

**Acquisitions** reviewed and/or approved ~4.5K requisitions, 228 contract packages, and the award of 138 contracts in FY2023 to support NCTR research and NCTR's annual Advanced Acquisitions Plan, Acquisitions Strategy, and conducts periodic audits and support for the Center's purchase card program. PRM also supported FDA via acquisitions system user testing, working groups, and change advisory boards to ensure efficient system revisions that met operational needs.

**Finance** served as the accuracy reviewers and funds approvers for all finance transactions. This included validating funds authorizations, tracking funds obligations and commitments, and providing data and forecasting for future financial needs. PRM reviewed and certified all Center travel, oversaw government credit cards, controlled payroll, and reviewed and approved all Center requisitions ensuring that appropriated funds aligned to financial policies and regulations.

**Operational Planning and Performance Management**, a Center-wide collaborative function, evaluated project-level planning costs against resource actual costs. PRM used this monthly monitoring to determine residual resource needs versus excess, providing leaders with key financial information and historic datasets to inform future resource needs.

**Budget Formulation and Execution** conducted financial operations to spend appropriations legally and responsibly in alignment with the Federal Budget Process to inform the President's Budget. Approximately 50 accounting transactions, such as reclassifications and G-schedules, were processed in FY2023. Staff managed reimbursable IAAs, shared allowances, and other external funds received in support of research.

PRM staff ensure that NCTR's financial requirements are understood, justified, and approved according to Appropriations Law and other federal and departmental guidance—resulting in over 99% of the Center's Congressional Appropriations being executed in a way that most benefits the American people.

### Other PRM Accomplishments

- Continued monthly Budget Analyst training sessions and initiated other outreach programs to be more accessible and to address additional training and support sessions, such as meet and greets, office hours, and individual or small group training sessions with the budget analysts and government credit card holders.
- Conducted evaluations for NCTR, such as organizational assessments, cost analyses, internal control assessments to support, inform, and improve long-term and short-term strategic planning.
- Led the development and analysis of the Center's performance budget through all phases of the Congressional budget process.
- Provided management advisory services, conducted analytical studies, supervised risk-management activities, and oversaw strategic and performance plans.
- Processed concepts and protocols to ensure complete and accurate cost of NCTR research projects.
- Provided data and responded to a variety of requests pertaining to NCTR research, including Government Accountability Office studies, annual economic reports, and annual collaborative reports.
- Assisted in the development and monitoring of Enterprise Performance and ensured that the Center specific performance measured within the performance plans of the Center Director, FDA Chief Scientist, and Commissioner are tracked and reported.
- Served as the technical point of contact and liaison for many of the Center's financial, acquisition and protocol processing systems and applications, and provided support as user testers and technical points of contact for other FDA systems such as Integrated Time and Attendance System and Unified Financial Management System.
- Evaluated, updated, and maintained modernized business processes. Coordinated and organized with NCTR staff to identify efficiencies and enhancements and worked with systems administrators both internally and externally to implement improvements. Developed new financial resource analysis techniques and advanced IT solutions to streamline business processes and automation workflows in all PRM processes where possible.

# By the Numbers (PRM)

| | |
|---|---|
| $11.4M | external funds managed by Budget Execution |
| $9.1M | internal discretionay funds managed |
| ~4.5K | requisitions reviewed/ approved |
| 138 | contracts awarded |
| 50 | data call responses |
| 50 | accounting transactions |

*PRM had the opportunity to attend an offsite team training event in Branson, MO, to explore ideas for teambuilding and conflict resolution, and to engage in open discussions about NCTR, OM, and PRM policies and procedures. The team defined better internal processing practices and will continue to explore concepts that might increase the support and collaboration with the Center's research divisions administrative support elements.*

## *Executive Programs and Services*

The Executive Programs and Services (EPS) branch is dedicated to being a valued business partner and leader by providing outstanding operational and strategic human capital services to support NCTR's mission and vision. In 2023, EPS accomplished goals involving recruitment, hiring, employee development, performance management, pay and leave administration, employee engagement, recognition programs, and property while serving a robust diverse workforce.

Supporting NCTR, the EPS staff actively identified and recruited talent from a diverse talent pool; promoted diversity, equity, and inclusion; provided training and technical assistance to employees; led the awards and recognition program; and participated in career fairs to expand the applicant pool by hosting career fairs for potential future talent and advertising job announcements on diverse social media platforms and job board platforms.

### EPS Personnel Accomplishments

The EPS staff accomplished the following recruitment efforts during 2023:

- Posted 53 job announcements
- Onboarded 18 staff, including 5 transfers from other federal agencies (CDC, EPA, Pine Bluff Arsenal, and USDA)
- Offboarded 17 staff
  - » 2 transfers to other federal agencies (NIH and EPA)
  - » 4 transfers to other FDA Centers (including CTP and CFSAN)
  - » 6 voluntary retirements
  - » 4 resignations
  - » 1 end temporary employment

### Career Fairs

Community engagement continues to be a priority for NCTR. In 2023, EPS took NCTR's message to the local community by attending career fairs at Little Rock Air Force Base and the University of Arkansas at Pine Bluff. EPS was able to interact with approximately 200 job seekers at these events.

### Diversity, Equity, and Inclusion (DEI)

In 2023, NCTR's DEI Committee sponsored the following events designed to promote and champion diversity, equity, and inclusion in the workplace:

- Coordinated and hosted a Pride Celebration Rainbow Shaved Ice event
- Organized the Hispanic Heritage Book Club to discuss works written by prominent Hispanic authors


*Pride Celebration Rainbow Shaved Ice Event*

# Office of Management

### *Executive Programs and Services (Cont.)*

- Supported the Blacks in Government (BIG) organization with a panel discussion during Black History Month on various historical black figures and their achievements
- Encouraged staff to identify and celebrate women who influenced their lives and to share stories, quotes, or words of wisdom from them as part of International Women's Day

**Federal Employee Viewpoint Survey**

During 2023, NCTR staff participated in the annual Federal Employee Viewpoint Survey (FEVS) to measure staff's perceptions on work experience, their agency, and leadership. The 2023 FEVS had a participation rate of 81.4% and the results afforded the FEVS workgroup an opportunity to enhance employee experience and engagement by hosting training seminars on topics such as, "Identifying and Avoiding Burnout in the Workplace," "Understanding Personalities in the Workplace," and "What is Emotional Intelligence?"

At its core, employee engagement is a union of intellectual, physical, and emotional energy—a state of mind, body, and spirit—at the workplace with favorable impact to both the individual and the organization. In addition to the DEI and FEVS initiatives, NCTR and EPS expanded workforce engagement through the following activities:

- **The Salvation Army Angel Tree**—Thanks to JL employees' donations, three vehicles full of toys were delivered to the Salvation Army to help six children in Arkansas
- **The Arkansas Food Bank**—JL staff signed up for 39 volunteer slots to sort and package over 24,000 pounds of food to benefit 4,800 families from across the state
- **Night at the Ballpark**—Over 175 tickets were purchased by JL employees to enjoy food and companionship while the Arkansas Travelers defeated the Springfield Cardinals

*OM staff volunteered at the Arkansas Food Bank in December*

These employee engagement activities promoted positive relationships across campus, provided opportunities for new employees to meet and interact with colleagues, and fostered an environment of cohesion and camaraderie across JL.

**Property Management Team Accomplishments**

The NCTR property team efficiently tracked, inventoried, identified, and disposed of excess property. The team partnered with stakeholders across the Center and inventoried over 3,500 pieces of equipment (valued at approximately $75M) and closed the 2023 annual inventory campaign with a score of 98.8%, a 1.94% increase from the FY2022 inventory.


*EPS was instrumental in organizing a volunteer day to the Arkansas Food Bank. Over 24,000 pounds of food were sorted and packaged by JL employees who signed up for 39 volunteer slots this holiday season at the Arkansas Foodbank. The work accomplished by the volunteers will benefit 4,800 families from across the state!*

## By the Numbers (EPS)

| | |
|---|---|
| 3500 | pieces of equipment inventoried |
| 98.8% | annual inventory campaign rate |
| 81.4% | FEVS participation rate |
| 53 | job announcements posted |
| 18 | staff onboarded |
| 17 | staff offboarded |

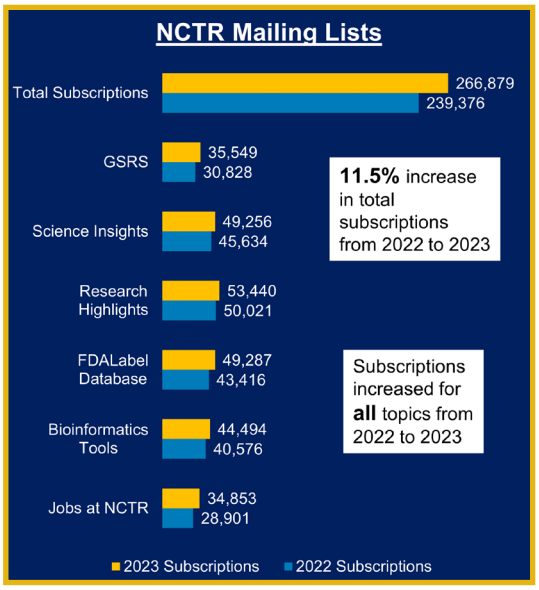
## *Communications Branch*

The NCTR Communications Branch (Comms) manages and develops NCTR's communications efforts with our internal and external stakeholders — promoting the important research conducted at NCTR. Some of these efforts include communicating with subscribers to NCTR mailing lists, writing, editing, managing web-content, providing graphics support, producing newsletters, producing videos, responding to requests for information and reports, preparing and editing conference presentations and posters, coordinating and supporting events. Comms represents NCTR on eight FDA-level councils/working groups.

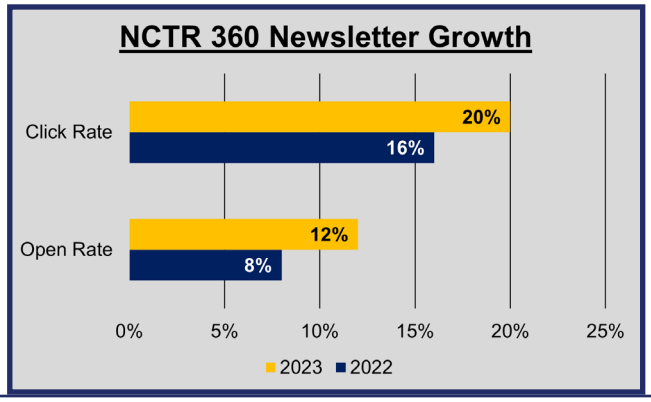
### FDA Internet

NCTR Comms manages over 250 web pages and 500+ media items on FDA's website at www.fda.gov/nctr. Some highlights include:

- PI Bio-Sketches — Maintaining bio-sketches for 120 NCTR principal investigators.
- NCTR Research Focus Areas — Keeping this content fresh as our focus areas change. For example, we added a topic page for AMR, and updated the AI4Tox and PHCE pages.
- Bioinformatics Tools — Supporting DBB to keep their content fresh and up to date.
- Science Advisory Board — Supporting the SAB Federal Designated Officer by editing and posting content.




***Subscribe to NCTR mailing lists here.***




## By the Numbers (Comms)

| | |
|---|---|
| 550+ | presentation slides reviewed and edited |
| 300+ | informative campus-wide emails sent |
| 200+ | scientific posters created |
| 141 | newsletter articles published |
| 41 | email bulletins sent to external stakeholders |
| 13 | Research Highlights/ Science Insights published |

### InsideFDA Intranet

Comms creates, publishes, and manages content on the FDA intranet. In 2023, this included ensuring the NCTR intranet homepage was current, socializing 214 events with staff at NCTR, Jefferson Labs, and FDA-wide. We also maintained the real-time "NCTR 360 LIVE" news feed. To increase employee engagement, Comms also created and shared four quizzes and two surveys with staff.

#### *"NCTR 360 LIVE" Internal News Outlet*

The NCTR 360 LIVE is a dynamic, comprehensive information outlet that provides real-time campus news and updates. Content in the NCTR 360 includes human interest pieces, employee spotlights, campus news, awards, cultural traditions, event write-ups and photos, messages from leadership, scientific accomplishments, and more.

> ***Article page views more than tripled between 2022 and 2023 (2,570 views compared to 8,002 views).***

### NCTR-, FDA-, and Public-Event Support

Comms supports in-person, virtual, and hybrid events through email promotions, content review, web promotion, remote-meeting coordination, event recordings, conference booth design and support, and more. NCTR Comms was instrumental in preparing NCTR's booth for the 2023 SOT annual meeting by coordinating the booth layout, creating literature handouts, designing and printing banners, and setting up the booth on-site (*page 12*). Comms also provided both virtual and in-person support for the hybrid 2023 NCTR Honor Awards Ceremony, including design, coordination, and setup.

# Office of Regulatory Compliance and Risk Management

***The mission of NCTR's Office of Regulatory Compliance and Risk Management (RCRM) is:***

- ***to ensure the safety and security of the Jefferson Laboratories employees***
- ***to ensure research conducted at the NCTR is compliant with state and federal regulations***
- ***to assist in the assurance of quality and integrity of the research data***

## Office Leadership

***Associate Director – Raj Nayak, Ph.D.***

## *Regulatory Compliance*

RCRM staff conduct comprehensive risk assessments of NCTR research protocols to:

- ensure regulatory compliance in chemical, biological, radiological, laser, and environmental safety
- maintain inventories of hazardous chemicals, biological agents and toxins, and controlled substances
- oversee safety of employees under the medical, animal surveillance, and industrial hygiene programs
- provide necessary job-related safety training to employees

In addition, RCRM also maintains the following compliance programs:

- AAALAC program accreditation
- Arkansas Department of Environmental Quality Air and Water safety programs
- Drug Enforcement Agency controlled substances
- EPA hazardous waste disposal
- FDA Office of Laboratory Safety (OLS)
- Nuclear Regulatory Commission (NRC) License
- Occupational Health Unit (OHU) Medical Surveillance Programs
- Occupational Safety and Health Administration employee health/accidents

RCRM staff manage campus security (physical security, badging, fingerprinting, background clearances, etc.), records management, archiving, and quality assurance.

## *COR Responsibilities*

RCRM staff serve as Contracting Officer Representatives (CORs) for multiple contracts, including waste recycling, security, Pine Bluff Arsenal-IAA, medical laboratory services, physician services, ORISE-IAA, paper shredding, and hazardous/medical waste disposal.

## *Customer Service*

RCRM provides consistent, reliable, and excellent customer safety and security-related services to the JL campus and FDA. During the recent pandemic, RCRM-OHU nurses worked closely with the FDA Contact Tracing Team to provide assistance to staff and management on COVID-19-related issues. RCRM staff routinely:


***RCRM sponsored an active shooter response seminar with 84 attendees (78 online and 6 in person)***

- provide safety updates through the JL Environmental, Safety, and Health Committee meetings
- respond to emails/phone calls/anonymous safety reporting
- advise staff on personal protective equipment
- oversee other safety programs such as hot work permits, confined space assessments, asbestos sampling, AlertFDA system, fire/tornado drills, preconstruction building safety and security, continuity of operations, and occupant emergency plans

## *Partnerships*

RCRM staff support the mission of the FDA OLS by assisting with and supporting their efforts to provide consistent and standardized guidelines, policies, procedures, and training across the Agency. RCRM staff also support the FDA Employee Safety and Occupational Health program organized under OFEMS by providing occupational health and medical services to all government and contract employees, as well as research training program participants. RCRM staff provide real-time data to OLS on the lab safety inspections and updating them on the various activities related to safety training, employee occupational health and accident investigations/reports, and environmental safety programs such as chemical hygiene, hazardous waste management, chemical fume hoods and biosafety cabinets, and biosafety/bloodborne pathogen risk controls. Upon request, RCRM staff review and test a variety of policy guidance documents for OLS, such as safety training modules, laboratory move guides, animal biosafety manuals, laboratory safety data initiative, guidelines for working in labs/vivaria during the COVID-19 pandemic, and FDA's Contact Tracing program.

## In 2023, RCRM Staff

- Conducted regulatory review of 150+ scientific protocols
- Certified 99 chemical fume hoods
- Maintained an inventory of 12,000+ hazardous chemicals at NCTR
- Certified 2 Laminar Flow Hoods, 3 Change Stations, and 95 Biosafety Cabinets
- Maintained an inventory of 7,400+ hazardous biological agents and toxins at NCTR
- Provided annual radiation safety training to 20 employees
- Provided lab safety, security, and records management training to 19 students (SSRP)
- Provided New Employee Safety Orientation training to 40 employees
- Provided physical exams and respiratory fit tests to over 300+ employees and 100+ flu shots
- Completed 90+ quality assurance reviews
- Completed 50+ Freedom of Information Act requests
- Badged 150+ employees and processed 160+ fingerprints (Security)
- Successfully addressed 25 HHS and FDA data calls
- Participated in high level OLS–Environmental and Occupational Safety and Health Programs (EOSH) monthly meetings
- Verified OLS monthly reports and annual progress reports for accuracy (RCRM compliance staff and OHU)
- Participated in the monthly (optional) and quarterly (required) FDA OLS Laboratory Quality Management System Working Group Meetings
- Participated in weekly (Administrative) and monthly (Official) meetings of the FDA Institutional Biosafety Committee
- Participated in the FDA OLS EOSH Training Survey
- Reviewed and provided feedback for the following FDA OLS Manuals/Guides/Trainings: General Biosafety Training, Laboratory Safety for Students and Interns Training, Opioid Exposure and Naloxone Use: FDA Workers Policy and Procedure, Personal Protective Equipment Guide, Hazardous Waste Management Manual, Laboratory Move and Renovation Preparatory Guidelines, Respiratory Protection Plan, Guide to Reproductive Health, EOSH Program and Contacts Guide
- Participated in the FDA OLS Culture of Safety Survey 2023
- Reviewed monthly FDA OLS Safety Updates

## By the Numbers

| | |
|---|---|
| 12000+ | hazardous chemicals inventoried |
| 7400+ | hazardous biological agents/toxins inventoried |
| 300+ | physical exams and respiratory fit tests provided |
| 150+ | scientific protocol regulatory reviews conducted |
| 100+ | flu shots provided |
| 90+ | quality assurance reviews |

## 2023 Select RCRM Accomplishments

- Created new RCRM SharePoint Site on FDA Intranet
- Updated RCRM operational summaries and JL Environmental Safety and Health manual
- Successfully completed FDA OLS Laboratory Safety audit. All 265 findings from 165 labs were addressed/completed by RCRM staff
- Successfully completed OLS Environmental Compliance audit. Awaiting report from OLS
- Successfully completed OLS Laser Safety “practice” audits
- Successfully completed NRC audit of our radiation safety program
- Successfully completed FDA OLS first ever Agency-wide standardized Laboratory Quality Management System Implementation Assessment
- Successfully completed three quarterly meetings with JL Radiation Safety committee and JL Environmental Health and Safety Committees
- Finalized NCTR Industrial Hygiene Program
- Completed and made operational new five-year security guards contract
- Successfully completed JL annual fire drills with Pine Bluff Arsenal Fire Department

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