National Center for Toxicological Research

Annual Report 2022

www.fda.gov/NCTR

Welcome to Our **ANNUAL REPORT** 2022

This report highlights NCTR's accomplishments for the 2022 calendar year (CY). 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.

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Center Director **MESSAGE**

Tucker Patterson, Ph.D.
NCTR Director

The U.S. Food and Drug Administration's (FDA) National Center for Toxicological Research (NCTR) is a laboratory research center in the Office of the Chief Scientist that supports the FDA-regulated product centers. For over 50 years, it has served to address the FDA's needs of non-biased, high-quality science accomplished through global collaboration, state-of-the-art training, and innovative scientific-based solutions. NCTR sets its vision on the FDA horizon to provide positive contributions, reliable data, and innovative tools that assist FDA in its public health mission.

In this annual report we will highlight the outstanding accomplishments of NCTR research scientists. We also will share how NCTR scientists continue to support FDA in generating essential data and advancing the innovative tools and approaches vital to the Agency's research capability and our ability to predict risk and efficacy.

In 2021, NCTR celebrated its 50th Anniversary and 2022 marked the beginning of what I consider to be another 50 years of outstanding scientific accomplishments. As the newly appointed Director, I am excited to lead the tremendous staff at NCTR who are devoted and dedicated to supporting FDA's public health mission and improving the quality of life for everyone.

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

- 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 more accurate and economic 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.
- Develops—or 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.

About NCTR

NCTR Expertise

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

NCTR Research Goals

1) Advance the scientific knowledge and research data required to support public health

2) Develop and evaluate the next generation of science and emerging technologies

3) Address emerging public health challenges (product contaminants, antimicrobial resistance, viruses)

4) Collaborate with FDA product centers and offices to address issues of regulatory concern

5) Promote global outreach and collaborative research

Facilities

500 acres
owned and operated by FDA

1 million+
square feet in 30 buildings

100+
experimental laboratories

75+
AAALAC-accredited laboratories

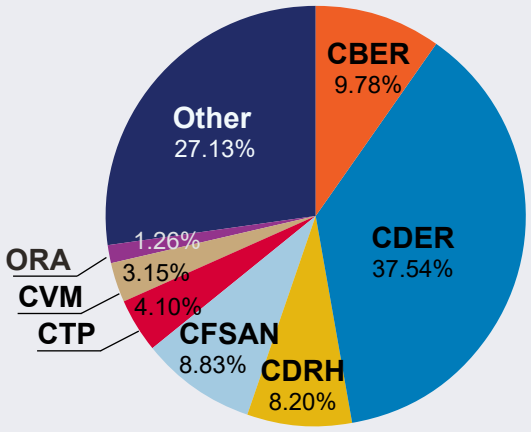
Evolving Scientific Areas

- ✓ Artificial intelligence (machine learning, text mining, in silico modeling)
- ✓ Microbiome and host interactions
- ✓ Microorganism detection in FDA-regulated products
- ✓ New alternative methods (NAMs)
- ✓ Omics (genomics, metabolomics, proteomics, epigenetics)
- ✓ Perinatal and maternal health
- ✓ Rare diseases
- ✓ Research addressing the unmet needs of minority and at-risk populations
- ✓ Translational and precision medicine

NCTR investigates new biomarkers of toxicity using traditional and innovative genomics, metabolomics, proteomics, epigenetics, and imaging technologies and approaches.

NCTR
BY THE NUMBERS

NCTR Collaborative Projects
(as of 12/31/2022)



Research Protocol Activity
By Calendar Year

	2019	2020	2021	2022
Manuscripts	135	162	144	**148**
Technical Reports	36	61	50	**39**
New Protocols	57	48	51	**47**

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.

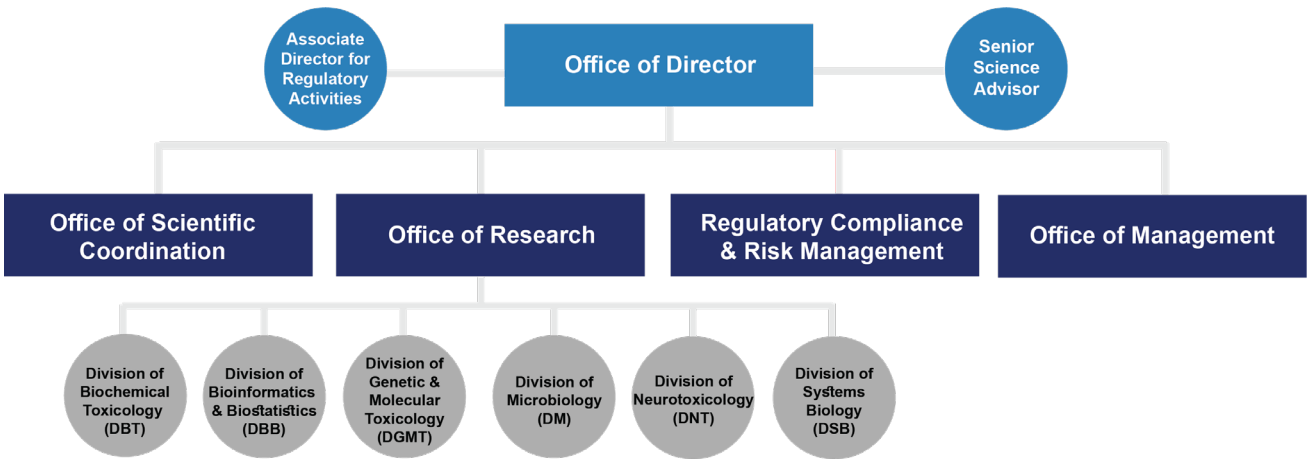
Explore the progress NCTR is making towards its strategic priorities.

Organizational Acronyms

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
OFEMS	Office of Facilities Engineering and Mission Support Services
OIMT	Office of Information Management and Technology
ORA	Office of Regulatory Affairs
OWH	Office of Women's Health
PHCE	Perinatal Health Center of Excellence
SBIA	Small Business and Industry Assistance

Organizations Outside FDA	
AAALAC	Association for Assessment and Accreditation of Laboratory Animal Care Intl.
ARA	Arkansas Research Alliance
AR-BIC	Arkansas Bioinformatics Consortium
ASTM	American Society for Testing and Materials
HESI	Health and Environmental Sciences Instititute
MAQC	Massive Analysis and Quality Control Society
MCBIOS	MidSouth Computational Biology & Bioinformatics Society
mQACC	Metabolomics Quality Assurance and Quality Control Consortium
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NTP	National Toxicology Program
ORISE	Oak Ridge Institute for Science and Education
UAMS	University of Arkansas for Medical Sciences
UTHSC	University of Tennessee Health Science Center

NCTR Organization



Office of the Director (OD)

Leadership

- Center Director – Tucker A. Patterson, Ph.D. (Acting March 2022 – March 2023)
- Senior Science Advisor – Gonçalo Gamboa da Costa, Ph.D.
- Associate Director for Regulatory Activities (ADRA) – Donna L. Mendrick, Ph.D.

Dr. Tucker Patterson speaks to NCTR staff at an all-hands meeting

2022 Select OD Publications

- "Emerging Technologies and Their Impact on Regulatory Science." *Experimental Biology and Medicine*
- "Machine Learning Models for Rat Multigeneration Reproductive Toxicity Prediction." *Frontiers in Pharmacology*
- "Machine Learning Models for Predicting Cytotoxicity of Nanomaterials." *Chemical Research in Toxicology*
- "Perspectives on the Evaluation and Adoption of Complex In Vitro Models in Drug Development: Workshop with the FDA and the Pharmaceutical Industry (IQ MPS Affiliate). *ALTEX*

2022 Office of the Director (OD) Select Outreach Events, Presentations and Publications

Dr. Patterson — 2022 Presentations

» CVM Science and Research Council – Summary of ongoing collaborative projects between NCTR and CVM

» CDER Research Governance Council – NCTR overview and current collaborative research projects with CDER

» Office of Orphan Product Development – NCTR overview

Dr. Mendrick — 2022 Presentations

» Drug Information Association Meeting Session, "The Translational Value of Animal Models in Rare Diseases" – *Perspectives on Evaluating New Tools for Regulatory Use*

» FDA 10th Annual Scientific Computing Days: Breakout Session, "AI and Its Use in the 3Rs" – *Looking Back 10 Years: AI and the 3Rs*

Dr. Mendrick — Chaired Events

» FDA Alternative Methods Working Group seminars (15 seminars)

» FDA Artificial Intelligence Working Group seminars (10 seminars)

» Microphysiological Systems (MPS) World Summit – Planning committee member, panel discussion co-chair, and poster judge

Outreach

Global Summit on Regulatory Science

The NCTR-established Global Summit on Regulatory Science (GSRS) is internationally recognized and consistently provides the space for international regulators, policy makers, and scientists to exchange views on how to develop innovative research methodologies and translate them into regulatory assessments. The goal of the GSRS is to engage the global research community and harmonize research strategies via collaborations that aim to build knowledge, promote regulatory science, define research needs, and strengthen product safety worldwide by training regulatory scientists. The GSRS is led by the Global Coalition for Regulatory Science Research (GCRSR), which is comprised of regulatory-science leaders from around the world.

GSRS22

The 12th Global Summit on Regulatory Science (GSRS22) was held in Singapore in October 2022. The Summit was co-hosted by the Singapore Food Agency (SFA) and the GCRSR. The theme for GSRS22 was "Advances in Nanotechnology for Food and Medical Products: Innovations, Safety, and Standards." There were presentations and workshops, with presenters from Australia, Brazil, Canada, China, EU, Italy, Japan, Switzerland, Singapore, United Kingdom, and the United States. GSRS22 highlights included, but were not limited to:

- Pre-recorded remarks by the U.S. FDA Commissioner
- Scientific poster displays
- Two different session tracks: Food and Drug/Medical Products
- Bioinformatics and Capacity-Building workshops

GSRS20 Manuscript

A summary manuscript of presentations and accomplishments of the 10th Annual Global Summit on Regulatory Science–"Emerging Technologies and their Impact on Regulatory Science" with presentations from over 50 scientists world-wide including a dozen FDA scientists–was published in January 2022 in *Experimental Biology and Medicine*.

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.

2022 SAB Meeting

NCTR's 2022 SAB meeting was held virtually in May 2022 over two days.

Watch recording of SAB – Day 1

Watch recording of SAB – Day 2

More information on the 2022 SAB meeting can be found on the website.

Outreach

NCTR Science Day

NCTR Science Day 2022 was held virtually in March with the goal of giving scientific staff at FDA headquarters and leadership in the FDA product centers the opportunity to:

» Discover the range and scope of NCTR's cutting-edge research;

» Interact and network with NCTR leadership and research staff; and

» Explore potential avenues for collaboration and greater alignment with center scientific priorities.

The day's agenda began with a one-hour segment dedicated to virtual poster session-viewing, in which 54 research staff shared how they are advancing the tools and approaches that are vital to FDA's ability to predict risk and efficacy.

Dr. William Slikker, former NCTR Director, provided a "State of the Center" overview of NCTR's capabilities and approaches to enhance collaborative research across the Agency to the 250+ virtual attendees. Acting FDA Chief Scientist, Dr. Jacqueline O'Shaughnessy, acknowledged that NCTR's research and contributions could be found across FDA and provided examples of ongoing collaborations between NCTR and other FDA centers and offices. The directors of NCTR's six research divisions and other research units provided examples of NCTR research activities and capabilities. The other FDA centers (CBER, CDER, CDRH, CFSAN, CTP, and CVM) and ORA also discussed their research needs and activities.

Following a discussion session with the FDA-only audience aimed at improving collaborations, a short awards ceremony was conducted, giving "FDA/NCTR Outstanding Collaborator Awards" to the research liaisons at the product centers for "significant contributions to the review of NCTR research concept papers and protocols, which are critical to ensure that NCTR conducts high-quality research that fulfills the FDA mission."

The day closed with a Q&A session for the presenters and a tribute video to Dr. Slikker's 44 years of service to FDA/NCTR.

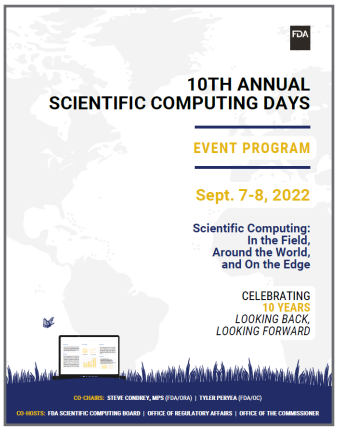
Arkansas Research Alliance (ARA) Project Scope Webinar Series

» "Studies of Virulence Characteristics in *Salmonella* and *Eschericia coli*" – Dr. Steven Foley, Director, Division of Microbiology. Dr. Foley was featured in a Research Matters (PDF) article in *Arkansas Money and Politics*.

» "Artificial Intelligence Approaches as Alternatives to Animal Studies" – Dr. Weida Tong, Director, Division of Bioinformatics and Bioststatistics.

Outreach

FDA Scientific Computing Days



FDA's 10th Annual Scientific Computing Days (SCD) was hosted by FDA's Scientific Computing Board (SCB), Office of Regulatory Affairs, and the Office of the Commissioner. This year's public SCD theme was "Scientific Computing: In the Field, Around the World, and On the Edge" and included keynote and guest speakers, a poster gallery, and various breakout sessions. An NCTR poster, titled "AnimalGAN: A Generative AI Alternative to Animal Clinical Pathology Testing," was selected as one of five featured posters.

The poster-selection process involved participants submitting their abstracts and the SCB reviewing and selecting the posters for inclusion in the FDA.gov poster gallery. The SCD participants then voted on their favorite posters prior to the event. The five posters with the most votes were featured in the SCD poster session with live presentations and those poster presenters participated in a 30-minute question and answer session.

NCTR Participation in FDA 2022 Scientific Computing Days

Breakout Session — ***AI and Its Use in the 3Rs*** **(Dr. Donna Mendrick, co-organizer)**

- "Looking Back 10 Years: AI and the 3Rs" – Dr. Donna Mendrick
- "Using Advanced Modeling Techniques for Building Robust, Transparent, and Interpretable Predictive Models. Decoding the Structure-Activity Relationship" – Dr. Svetoslav Slavov
- "Using AI to Simulate Clinical Chemistry and Hematologic Data of Untested Compounds (AnimalGAN)" – Dr. Weida Tong

Breakout Session — ***Leveraging Edges Using Interdisciplinary Omics***

- "Metabolomic and Proteomic Biomarkers for the Prediction of Outcomes in Dialysis-Dependent AKI Patients" – Dr. Li-Rong Yu

For more information on FDA Scientific Computing Days, click here.

Poster Sessions

- "AnimalGAN: A Generative AI Alternative to Animal Clinical Pathology Testing" – Drs. Xi Chen, Zhichao Liu, and Weida Tong ****This poster won the #4 spot of the top 5 posters.*** View the poster (PDF) and watch the presentation.
- "The Adaptability of using AI for Drug Safety Assessments within Regulatory Science: A Case Study of DeepDILI" – Drs. Skylar Connor, Ting Li, Zhichao Liu, Weida Tong
- "Classifying Unformatted Texts into Organized Sections Using BERT Language Modeling" – Drs. Magnus Gray, Joshua Xu, and Leihong Wu
- "Medical Information Mart for Intensive Care (MIMIC-III): A Real-World Data Foundation for Reproducible Artificial Intelligence Machine Learning Research" – Drs. Paul Rogers, Dong Wang, and Zhiyuan Lu
- "Using Advanced Modeling Techniques for Building Robust, Transparent, and Interpretable Predictive Models" – Dr. Svetlyo Slavov

Outreach

Other Outreach Events

European Food Safety Authority One Health Conference — Dr. Sangeeta Khare, research microbiologist in the Division of Microbiology, participated as a speaker in the session "Microbiomes, Chemicals and Health: Unravelling an Intricate Triad." The title of her presentation was "Unlocking the Potential of Host-Microbiome Interaction in the Risk Assessment." In addition to presenting, Dr. Khare also served as a panel member in discussions on "Microbiome and Host Health Interplay." Watch Dr. Khare's interview by the EFSA communication team describing the importance of the human microbiome from a One Health perspective.

11th International Conference on Antimicrobial Agents in Veterinary Medicine — "In Vitro Studies on the Impact of Tetracycline Exposure on Resistance Plasmid Transfer in *Salmonella enterica*" was presented by Dr. Steven Foley, Director, Division of Microbiology. The talk highlighted key research findings on how antibiotic exposures can impact the spread of antibiotic resistance in *Salmonella*, a leading cause of bacterial foodborne illness.

MAQC 2022 Conference — The 5th annual meeting of the MAQC Society was co-sponsored by FDA and NCTR. Dr. Tucker Patterson, NCTR Director, and Dr. Namandjé Bumpus, FDA Chief Scientist, gave the welcome and opening remarks. Other NCTR scientists chaired or presented sessions:

DBB

- "Real World NGS Challenges" – Dr. Joshua Xu (Session Chair)
- "AI or Animal—A Reproducibility Perspective" – Dr. Weida Tong
- "Reproducible AI for Supporting Regulatory Applications—A Case Study" – Dr. Ting Li
- "Enhancing Reproducibility of Language Models in BERTox" – Dr. Leihong Wu
- "Reproducible Toxicogenomics Analysis in the Three-Sample Scenario" – Dr. Dongying Li
- "NCTR Indel Calling Challenge from Oncopanel Sequencing Data" – Dr. Binsheng Gong
- "Targeted RNA-Seq for Small Variant Detection to Enhance Precision Medicine" – Dr. Dan Li
- "Integrated Calling and Evaluation of Gene Fusion Detection by Targeted RNA Sequencing of Reference Samples with Long and Short Reads" – Dr. Joshua Xu

DGMT

- "Evaluation of mutagenic susceptibility of different stages in germ cell development of *Caenorhabditis elegans* using next generation sequencing" (Poster) – Dr. Tao Chen

Metabolomics Association of North America Conference — "A Community-Led Initiative to Strengthen Quality Assurance and Quality Control Practices and Reporting in Untargeted Metabolomics Research" was presented by Dr. Richard Beger, Chief of the Omics, Modeling, Imaging, and Chemistry Branch in the Division of Systems Biology. Dr. Beger also serves as the Chair for the **International Metabolomics Quality Assurance and Quality Control Consortium (mQACC)**; mQACC members prepared and presented a "QC Best Practices in Metabolomics Workshop" at the **Metabolomics 22** international conference held in Valencia, Spain.

Research Focus Areas

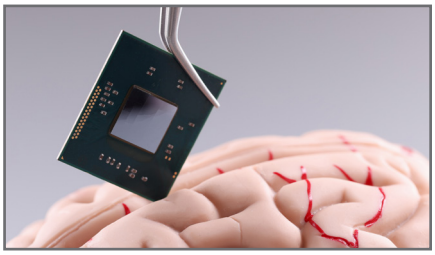
Alternative Models

Organ-on-a-Chip Technology

Novel non-animal and human-specific technologies like organ-on-a-chip technology for disease modeling are priorities for research agencies like the National Institutes of Health (NIH) and private research companies. The likelihood that investigational new drugs containing pre-clinical studies using these technologies is greatly increasing. Implementing these technologies at NCTR will provide FDA with expertise to conduct internal studies and interpret and evaluate external studies where these technologies are employed. This will aid the review process of potential treatments of various conditions such as Alzheimer's Disease (AD), using AD-on-a-chip technology, and drug-induced liver injury (DILI), using DILI-on-a-chip technology—both discussed in detail in the sections below. Successfully implementing a translational AD model at NCTR will allow the Agency to analyze the effects of potential drugs, biologics, and/or medical devices being developed for AD treatment. Another aim of this project is to produce a "healthy" brain-on-a-chip model. This model would provide a screening platform to assess the potential toxic effects of any drug, biologic, or medical device for treating central nervous system (CNS)-related disorders. This project may greatly increase FDA capabilities to conduct studies on CNS-related disorders and the project is slated to be active into fiscal year (FY) 2024.

Disease-on-a-Chip Technology

NCTR scientists collaborated with Emulate, Inc. to support alternative methods by developing AD-on-a-chip technology. Researchers successfully established protocols to differentiate endothelial cells, neurons, astrocytes, and pericytes from a healthy control and a patient with AD. Isogenic chips were constructed and used to validate a battery of tests associated with neurovascular functions. Validated tests included:



- paracellular permeability to molecules of different sizes (0.5 kDa and 3 kDa),
- function of the membrane-bound transporter P-glycoprotein,
- accumulation and production of amyloid beta and tau,
- western blot analysis for proteins related to neurovascular functions,
- immunocytochemical analysis of proteins related to blood-brain-barrier integrity and function of transporters.

This battery of tests will be used to evaluate AD-like pathology on the brain-on-a-chip.

Drug-Induced Liver Injury

Another ongoing alternative-model project at NCTR has the potential to establish a novel in vitro (non-animal) model to investigate the changes of both conventional and investigational DILI biomarkers (indicators of biological health or disease state). The data may help FDA better assess the ability of the liver-on-a-chip platform to predict idiosyncratic DILI—a rare disease that develops independently of drug dose, route, or duration of administration. DILI accounts for half of the U.S. acute liver-failure cases and represents a significant public-health issue, partially due to the limitations of currently used DILI biomarkers. New biomarkers identified during this liver-on-a-chip study are expected to complement the existing DILI biomarkers to help improve drug safety and promote public health.

Read more about NCTR's research focus areas.

Research Focus Areas

Artificial Intelligence and Bioinformatics

AI4Tox

NCTR researchers created AI4Tox, a new program that aims to apply the most advanced artificial intelligence (AI) methods to develop new tools to support FDA regulatory science and strengthen the safety review of FDA-regulated products. The program consists of four initiatives:

1. AnimalGAN – develop virtual animal models to simulate animal-study results using AI.
2. SafetAI – develop novel deep-learning methods for toxicological endpoints that are critical to the safety review of drug candidates before entering clinical trials.
3. BERTox – apply advanced AI-powered natural language processing to analyze FDA documents for improved efficiency and accuracy of information retrieval and toxicity assessment.
4. PathologAI – analyze histopathological data from animal studies to advance digital pathology in preclinical application.

AI Models

An artificially intelligent pregnant-woman modeling suite was initiated with an antihypertensive drug as the first case-study drug. Because there is a lack of real-world pregnancy data available, a validated PBPK population model is being used to generate data to train the AI model. Additional drugs will be tested based on data available within our in-house pregnancy pharmacokinetic database.

FDALabel – An FDA Drug Labeling Search Tool

The FDALabel database is a web-based application used to perform full-text and customizable searches of over 144,000 human prescription, biological, over-the-counter, and animal-drug labeling documents. FDALabel was updated to v2.7 in 2022 in a collaborative effort between CDER and NCTR's Office of Scientific Coordination and Division of Bioinformatics and Biostatistics. New features and enhancements released in this version include:

1. Drug-labeling data updated weekly,
2. MedDRA (Medical Dictionary for Regulatory Activates) terminology report available for each drug-labeling document, and
3. Biological and product link to Purple Book.

Antimicrobial Resistance

NCTR scientists were successful at removing representative plasmids from different bacterial strains and are working to optimize the approaches to make them more user friendly. The scientists are completing assessments on the impact of plasmid removal on bacterial survival and growth (*Frontiers in Microbiology*). Dr. Dereje Gudeta presented at NCTR Science Day and FDA Foods Conference describing the results of the project to date.

Cannabidiol Exposure

Preliminary data compiled on cannabidiol (CBD) exposure in the developing brain included gestational measures, early pup measures of development; behavioral data through the equivalent of young adulthood; and clinical-chemistry, neurochemistry, and protein-chemistry data. A final manuscript is expected to be ready for submission by mid-2023. Preliminary data regarding this research was presented at the 61st Annual Society of Toxicology meeting.

Research Focus Areas

Opioids

NCTR constructed a database of opioid receptors' agonistic and antagonistic activity derived from experimental data. The resulting Opioid Agonists/ Antagonists Knowledgebase (OAK) contains approximately 400,000 data points for four opioid receptors. Sophisticated search functions were implemented including text, numerical, and chemical structure/substructure searching. In addition, browsing functions such as narrowing search results, outputting data, and linking to other public databases were added to OAK.

NCTR researchers also finalized data regarding 3-dimensional molecular modeling of opioids and other chemicals. In 2022, a manuscript was published in the *Journal of Molecular Structure*.

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.

The PHCE Seminar Series was established in 2022 and consists of two to three seminars annually. Each hour-long virtual event features two speakers currently involved in PHCE-funded research. Each presentation provides background and research updates and impediments in ongoing studies. Additionally, NCTR hosts an annual PHCE meeting. At the two-day meeting in 2022, all principal investigators of PHCE-funded ongoing work presented the status and progress of their specific perinatal-related research. Both meetings were advertised FDA-wide and collaborators external to the FDA were invited to attend.

- 4 first-year projects funded in FY22 (PIs representing CDRH and CDER)
- 10 second-year projects continued in FY22 (PIs representing CBER, CDER, CVM, OC, and NCTR)
- 16 articles published in CY22

Select PHCE Articles Published in 2022

"Developing an In Vitro to In Vivo Extrapolation (IVIVE) Model to Predict Human Milk-to-Plasma Drug Concentration Ratios." *Molecular Pharmaceutics*

"Evaluation of the Robustness of Cerebral Oximetry to Variations in Skin Pigmentation Using a Tissue-Simulating Phantom." *Biomedical Optics Express*

"Improving Development of Drug Treatments for Pregnant Women and the Fetus." *Therapeutic Innovation & Regulatory Science*

"Zika Virus Infection and Antibody Neutralization in FcRn Expressing Placenta and Engineered Cell Lines." *Vaccines*

Read more information about the PHCE and its progress.

Research Focus Areas

COVID-19 Response

NCTR completed several collaborative studies in the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mouse model to assess the effect of SARS-CoV-2 in pregnant animals and their offspring. Specifically, studies were completed in collaboration with the University of Tennessee Health Science Center (UTHSC), which provided an assessment and characterization of the SARS-CoV-2 mouse model, focusing on determining the appropriate viral dose in non-pregnant animals. Additionally, a study to evaluate the inactivation of SARS-CoV-2 in tissues collected from exposed non-pregnant animals was completed. This study was necessary to facilitate the safe transfer of virus-inactivated tissues from biosafety level (BSL)-3 (more containment required) to BSL-2 laboratories for safe downstream histopathological and biomarker assessment. The results from these studies will aid decision making in ongoing studies using pregnant animals.

NCTR scientists also successfully established a mouse breeding colony (hACE2-KI) to provide the time-mated animals (animals with a precisely known mating date) needed to accomplish the overall aims of the protocol. These genetically altered mice express the receptor used for cellular entry by SARS-CoV-2 in humans; successfully establishing a colony will allow for the study of not only the effects during pregnancy, but also potential antiviral therapies. Currently, a pilot study is in progress to produce timed-pregnant animals and harvest tissue at various gestation days for histopathological assessment and detailed characterization of the hACE2 receptor expression in different maternal tissues, fetal tissues, and maternal/fetal interfaces tissues (e.g., endometrial tissue, the placenta, etc.). The results from this pilot study and the other previously completed studies are being used to continue assessment on the effect of SARS-CoV-2 in pregnant animals and their offspring.

- 11 articles published since pandemic began
- 20 active COVID-related projects
- 4 projects in development

Select Articles Published in 2022

"AI-Powered Drug Repurposing for Developing COVID-19 Treatments." *Reference Module in Biomedical Sciences*

"Evaluation of the Mutagenic Effects of Molnupiravir and N4-hydroxycytidine in Bacterial and Mammalian Cells by HiFi Sequencing." *Environmental and Molecular Mutagenesis*

"NeuroCORD: A Language Model to Facilitate COVID-19-Associated Neurological Disorder Studies." *International Journal of Environmental Research and Public Health*

"Applying Imaging Mass Spectrometry to Define the *N*-glycan Profiles of Co-localized Virus and Immune Cell Infiltrates in Post-COVID-19 Infected Lung Autopsy Tissues." *Frontiers in Analytical Science*

"Enhanced Virulence and Waning Vaccine-Elicited Antibodies Account for Breakthrough Infections Caused by SARS-CoV-2 Delta and Beyond." *iScience*

NCTR scientists developed a method to detect SARS-CoV-2 ribonucleic acid (RNA) in wastewater (***page 22***) and have applied it to select metropolitan areas in Arkansas. A paper was published in July 2022 summarizing the findings in *Science of The Total Environment*. Wastewater analysis can detect an increasing number of variants. This is important because strains like BA.5 evade immunity from patients with previous COVID-19 infections and/or vaccinations and are, therefore, more easily spread.

For more NCTR COVID-19 Publications, click here.

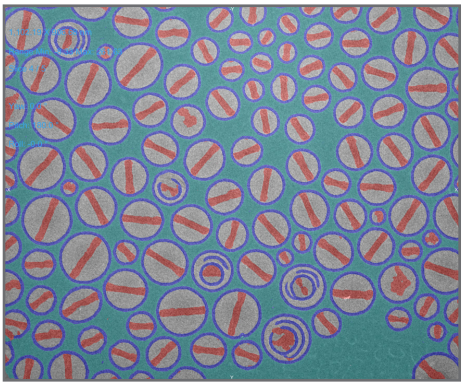
Research Focus Areas

Nanotechnology

Scientists from the Nanotechnology Core Facility (NanoCore) (***page 19***) developed four Test Method Standards in Nanotechnology that were published by the American Society for Testing and Materials (ASTM) International:

1. **E3297-21** Standard Test Method for Lipid Quantitation in Liposomal Formulations Using High Performance Liquid Chromatography with a Charged Aerosol Detector
2. **E3323-22** Standard Test Method for Lipid Quantitation in Liposomal Formulations Using High Performance Liquid Chromatography with an Evaporative Light-Scattering Detector
3. **E3324-22** Standard Test Method for Lipid Quantitation in Liposomal Formulations Using Ultra-High-Performance Liquid Chromatography with Triple Quadrupole Mass Spectrometry
4. **E3351-22** Standard Test Method for Detection of Nitric Oxide Production In Vitro

This collaborative research effort was conducted under the Inter Agency Agreement (IAA) with NIEHS and supported by the FDA Nanotechnology Task Force, FDA product centers, stakeholders, and subject matter experts from U.S. government agencies, academia, and industry. International Test Method Standards are an invaluable resource for both FDA and industry to protect and promote public health. These standards will increase predictability, streamline pre-market review, and facilitate new product entries to market.



The NCTR NanoCore team conducted research supporting collaborative consensus standards-development for liposomes.

NanoDay 2022

CDER's SBIA collaborated with NCTR to organize the FDA NanoDay Symposium 2022. The symposium, open to the public, addressed the drug development of products that contain nanomaterials in their formulation, and presented reviewer perspectives on laboratory efforts to better understand challenges to manufacture products that contain nanomaterials.

Over 3,500 participants from 97 different countries attended the FDA NanoDay Symposium 2022 as speakers addressed topics such as:

- Chemistry Manufacturing and Controls (CMC) Guidance For Development of Products that Contain Nanomaterials
- Nonclinical Perspective on Developmental of Drug Products Containing Nanomaterials
- Development and Characterization of Generic Drug Products Containing Nanomaterials
- Considerations for the Quality, Safety, and Efficacy of Prophylactic Lipid Nanoparticle mRNA Vaccines
- Safety Evaluation of Food-Contact Substances Containing Nanomaterials
- Nanomaterial Standards Development at FDA
- Future of Continuous Manufacturing of Drug Products Containing Nanomaterials

Dr. Anil Patri, NCTR NanoCore Director and chair of the FDA Nanotechnology Task Force, presented the welcome message and discussed the expanding field of nanotechnology and nanomaterial standards development at FDA. Dr. Patri also participated in the question-and-answer session where 121 questions were submitted by the live audience.

Read more information about Nanotechnology at FDA and NCTR.

NCTR
Research Offices and Divisions

The NCTR Research Offices and Divisions work closely in a seamless effort to support FDA's mission to bring safe and efficacious products to the market rapidly and to reduce the risk of adverse health effects from products currently on the market.

- ***Office of Scientific Coordination*** – **Bradley Schnackenberg, Ph.D., Associate Director**
- ***Office of Research***
  - Division of Biochemical Toxicology – **Frederick A. Beland, Ph.D., Division Director**
  - Division of Bioinformatics and Biostatistics – **Weida Tong, Ph.D., Division Director**
  - Division of Genetic and Molecular Toxicology – **Robert Heflich, Ph.D., Division Director**
  - Division of Microbiology – **Steven Foley, Ph.D., Division Director**
  - Division of Neurotoxicology – **John Talpos, Ph.D., Division Director**
  - Division of Systems Biology – **Laura Schnackenberg, Ph.D., Division Director**

NCTR encourages the research community to reach out to NCTR Principal Investigators to explore collaborative research opportunities. To find potential collaborators by research area, Search All Bio-Sketches Using "Find."

Office of Scientific Coordination (OSC)

Office Leadership

- Associate Director – Bradley Schnackenberg, Ph.D.
- Analytical Chemistry – Matthew Bryant, Ph.D.
- Microsurveillance – Sung Guk Kim, Ph.D.
- Veterinary Services – Pamela Mack, DVM, MS, DACLAM
- Nanotechnology Core – Anil Patri, Ph.D.

OSC provides the professional support necessary to conduct toxicology studies in support of FDA's and NCTR's research mission. This support is provided by the following support groups.

Analytical Chemistry

Analytical Chemistry research and support are conducted by trained staff and using state-of-the-art instrumentation to process a wide range of samples. Test articles and their metabolites are evaluated in blood, tissue, or urine to provide measures of exposure. Genotoxic compounds are tested by measuring DNA adducts. The high quality of studies at NCTR is ensured by 1) verifying test-article identity and purity, 2) certifying concentration and stability of test articles in dosing solutions and vehicles, and 3) surveilling animal-study materials (bedding, water, and diet) performed routinely.

Experimental Support

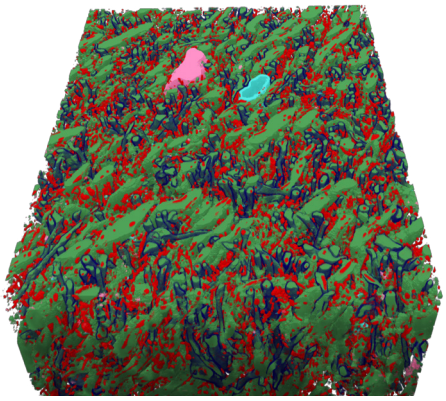
Experimental Support staff provide computer-based support for animal studies. The staff review study protocols and works with research and support staff to enter study parameters in the animal-data collection system, review data, and generate reports at the conclusion of the study.

Microbiological Surveillance Laboratory

The Microbiology Surveillance Laboratory staff ensure the research animals, environment, food, bedding, and test articles are free from opportunistic pathogens. The lab 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 next-generation sequencing. The laboratory staff also support other microbiology-related research studies from the research divisions.

Nanotechnology

The 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, including electron, atomic force and optical microscopy, scattering, diffraction, spectroscopy, fractionation, chromatography, and elemental analysis facilities 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.



Serial Electron Microscopic Analysis of the Hippocampus from an Alzheimer Transgenic Rat

Statistics

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

In 2022, OSC scientists contributed to the following selected publications:

- The NCTR/ORA Nanotechnology Core Facility (NanoCore)—supported by NTP and stakeholder involvement from government agencies, academia, and industry—developed documentary standards for nanomaterial characterization methods through the ASTM E56 subcommittee on Nanotechnology and ISO Technical Committee 229 (**Page 17**).
- The NCTR Microbiology Surveillance Unit (in collaboration with NCTR's Division of Microbiology) published five contributions to *Microbiology Resource Announcements* (**page 27**).

Veterinary Services

Veterinary Services staff play a key role in the research at NCTR, where they 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 participate in the research by advising study 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 accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC) since 1977.

OSC Service Contracts

Animal Care — provides study support to husbandry, environmental enrichment of all animals, formulation and administration of test articles, sample collection, and data collection. Works with the veterinary staff and the IACUC to ensure health and welfare of the animals.

Pathology Services — maintains onsite contract for veterinary pathology and histopathology services. Maintains a staff of three veterinary pathologists and a highly trained staff that provides NCTR with services including: clinical pathology, rigorous pathology examination, and complete histopathology and pathology reports for each study.

Equipment Maintenance and Repairs — supports 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.

2022 Select OSC Accomplishments

» **OSC scientists presented nine posters at 2022 NCTR Science Day.**

» **OSC collaborated with DBB and CDER to release the updated FDALabel v2.7. New features focused on improved interfaces and enhanced search capabilities. OSC hosted the first annual FDA-wide FDALabel virtual training with over 300 participants (page 14).**

» **OSC Analytical Chemistry Unit supported internal and collaborative studies:**

- **Developed analytical methodology and conducted the analysis of CBD and two of its major oxidative metabolites in rat plasma and brain (*In support of DNT*).**
- **Developed gas chromatography/mass spectrometry (GC/MS) and GC with flame-ionization detection (GC-FID) methods for the analysis of 1,4-dioxane to verity the concentration of a tritiated 1,4-dioxane sample used to study skin penetration of this compound (*In support of DBT*).**
- **Developed GC/MS methodology for the accurate quantitation of nicotine, propylene glycol, and vegetable glycerin. This methodology was used to analyze filter and exposure site samples from cigarette smoke and electronic nicotine delivery system (ENDS) vapors (*In support of DGMT and CTP*).**

» **Veterinary Services coordinated successful independent site visits by AAALAC and NIH's Office of Laboratory Animal Welfare for NCTR's animal care and use program and facilities.**

Division of Biochemical Toxicology (DBT)

Division Leadership

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

2022 Select DBT Accomplishments

Male Reproductive Toxicities Induced by Cannabidiol and Its Main Metabolites in Vitro

Researchers at NCTR, in collaboration with scientists from CFSAN, investigated potential male reproductive toxicities and their underlying mechanisms induced by cannabidiol (CBD) and its main metabolites—7-carboxy-CBD and 7-hydroxy-CBD—using immortalized mouse Sertoli cells and primary human Sertoli cells. Study results showed that CBD and its main metabolites can inhibit cellular proliferation in mouse and human Sertoli cells. The molecular mechanisms underlying CBD-induced cytotoxicity in primary human Sertoli cells were investigated further, using a transcriptomic approach with mRNA sequencing analysis. The results showed that CBD exposure mainly disturbs DNA replication, cell cycle, and DNA repair-signaling pathways and induces cellular senescence (state where cells do not die, but stop multiplying) in primary human Sertoli cells. These findings will help the FDA better define safety concerns regarding CBD (*Food and Chemical Toxicology*).

In 2022, DBT scientists contributed to or participated in the following outreach events:

Presentations

- 2022 NCTR Science Day (12 presentations)
- Society of Toxicology 2022 Annual Meeting (4 presentations)
- South-Central Chapter of the Society of Toxicology 2022 Annual Meeting (4 presentations)
- FDA Foods Program Regulatory Science Conference (2 presentations)
- 21st International Congress of the European Society of Toxicology In Vitro
- American College of Clinical Pharmacology Annual Conference
- The American Society for Virology's 41st Annual Meeting
- National Postdoc Association Annual Conference
- NIH/FDA COVID-19 Research Workshop

Scientific Journal Editors

- *Journal of Environmental Science and Health, Part C: Toxicology and Carginogenesis* (Editor-in-Chief, Associate Editor)
- "Pharmacology, Toxicology, Pharmaceutical Sciences" section of *Data in Brief* (Section Editor)
- *Toxicogenomics* (Associate Editor)
- Specialty section of *Frontiers in Genetics*, *Frontiers in Toxicology* (Associate Editor)
- *Frontiers in Environmental Science* (Associate Editor)

Memberships

- Organisation for Economic Co-operation and Development, Expert Group in Skin Absorption
- External Advisory Board, Masonic Cancer Center, University of Minnesota
- International Agency for Research on Cancer Working Group to Evaluate the Carcinogenic Hazards to Humans (aspartame, methyl eugenol, and isoeugeol), Experimental Carcinogenesis Subgroup

Lecture Series

- Organized NCTR Summer "Lunch and Learn" Lecture Series for 2022 ORISE Summer Student Program
- UAMS Systems Pharmacology and Toxicology T23 Program (Invited training faculty staff member)

Toxicological Evaluation of Brominated Vegetable Oil in Sprague-Dawley Rats

Researchers from NCTR, in collaboration with scientists from CFSAN, investigated potential toxicities from ingesting the food additive, brominated vegetable oil (BVO), using a rat model. Study findings expanded upon previous observations in rats and pigs that oral exposure to BVO is associated with increased tissue levels of inorganic and organic bromine and that the thyroid is a potential target organ of toxicity. This research and its findings will help FDA better define safety concerns regarding BVO. A paper reporting the study findings was published in *Food and Chemical Toxicology*.

Temporal Dynamics of SARS-CoV-2 in Wastewater Influent

NCTR scientists, in collaboration with the Arkansas Department of Health and UAMS, developed a method to monitor the presence of COVID-19-causing SARS-CoV-2 virus and its genetic variants in local wastewater in Little Rock and Pine Bluff, Arkansas. Using this method, researchers were able to identify the SARS-CoV-2 variants, such as Delta and Omicron, in the wastewater that were responsible for epidemic outbreaks. The viral titers found in the wastewater correlated with the number of COVID-19 clinical cases. These findings support the use of wastewater surveillance as a reliable complementary tool for monitoring SARS-CoV-2 and its genetic variants at the community level and can serve as an early indicator of viral spread and the emergence of new variants. The study findings were published in *Science of The Total Environment*.

Ongoing Research Projects

- Assess the developmental reproductive toxicity of metformin and glyburide
- Assess the epigenetic effects of the human food additive food-grade titanium dioxide in vitro
- Determine sex differences in immune responses to nanoparticles in vitro
- Develop an artificially intelligent virtual pregnant-woman modeling suite to support regulatory decisions
- Develop a first-generation in-house FDA pregnancy PBPK model-based tool to enhance the safety and efficacy of therapeutic agents in the perinatal period
- Evaluate the fetal and neonatal toxicokinetics of C6-fluorotelomer alcohol
- Analyze SARS-CoV-2 antibodies in human plasma using flow cytometry
- Identify genomic and genetic determinants of the susceptibility to non-alcoholic fatty liver disease (NAFLD) and NAFLD-related liver cancer
- Conduct high-throughput functional screens and mechanistic analysis of microRNAs that regulate chemotherapeutic resistance in ovarian cancer
- Evaluate the percutaneous absorption of the cosmetic contaminant 1,4-dioxane
- Evaluate the percutaneous absorption of the sunscreen component avobenzone
- Assess the performance of 3D-bioprinted human-skin equivalents for in vitro dermal-absorption testing of FDA-regulated drugs and cosmetic ingredients used for dermal and transdermal applications
- Evaluate the pharmacokinetics of nicotine in Sprague-Dawley rats
- Evaluate the pharmacokinetics of cannabidiol and its major metabolites in pregnant Sprague-Dawley rats and their pups exposed orally to cannabidiol
- Evaluate the pharmacokinetics of CBD upon dermal exposure in Sprague-Dawley rats
- Study the relationship between liver epigenomic phenotype and susceptibility to non-alcoholic steatohepatitis
- Evaluate the selection of complex mixtures for toxicological assessments
- Surveil SARS-CoV-2 in wastewater as a complementary tool to estimate the viral spread in Arkansas
- Stimulate innovation in clinical evaluations and personalized medicine to improve patient outcomes with triple-negative breast cancer

Division of Bioinformatics and Biostatistics (DBB)

Division Leadership

- Division Director – Weida Tong, Ph.D.
- Bioinformatics Branch Chief – Huixiao Hong, Ph.D.
- Biostatistics Branch Chief – Dong Wang, Ph.D.
- Scientific Computing Branch Chief – Edward Bearden
- Review-to-Research (R2R) Branch Chief – Joshua Xu, Ph.D.

2022 Select DBB Accomplishments

» Completed both phases of NCTR-driven Indel Calling (insertions and deletions in the cancer genome) Challenge in collaboration with PrecisionFDA, an FDA public-computing platform to advance precision medicine. Top performers were announced in a special session at the FDA/NCTR – MAQC 2022 conference out of 115 valid submissions.

» Awarded three FDA-level awards: Chief Scientist Publication, Group Excellence for Sequencing Quality Control Phase 2 (SEQC2) Team, and Outstanding Inter-Center Scientific Collaboration for SmartTemplate.

» Presented Research-to-Review (R2R) program at the inaugural FDA Digital Transformation Symposium public meeting with over 1,000 online participants.

» Published 45 papers in 2022, including a paper selected as a "Spotlights" feature in *ACS Chemical Health & Safety*.

» Received first- and second-place awards for the 2022 Environmental Mutagenesis and Genomics Society's Bioinformatics Challenge.

» Awarded FDA intramural-research grants for projects with topics including:
- Artificial Intelligence (AI) bias
- Big data and women's health
- COVID-19 and its variants

» Research featured in story on Dr. Weida Tong in *Elsevier Connect*.

In 2022, DBB scientists contributed to or participated in the following outreach events:

- **12th Annual Global Summit on Regulatory Science** – Dr. Weida Tong served as GSRS22 Conference Coordinator.
- **ARA Project Scope** – Dr. Weida Tong was featured at the ARA Project Scope webinar.
- **AR-BIC Virtual Meeting** – Executive Summary (PDF).
- **FDA/NCTR – MAQC 2022 Conference** – NCTR co-sponsored the conference.
- **FDA 10th Annual Scientific Computing Days** – four DBB posters were presented with one poster winning the #4 spot of the top 5 posters; one DBB breakout session (*page 11*).
- **MCBIOS 18th Annual Conference** – Dr. Joshua Xu served as conference chair and DBB scientists presented or chaired seven subsessions.
- **NCTR Science Day** – seven DBB posters were presented.

Ongoing Research Projects in Five Focus Areas

1. Regulatory Applications and Support

» Collaborating with CDER to:
- Support the Data Analysis and Search Host (DASH) to manage the lifecycle from investigational new drug (IND) submission to new drug application (NDA).
- Develop Smart Template System (STS) to automatically extract regulatory information from drug reviews and store it in an easily searchable database.
- Manage and update FDA drug labeling documents for query and research (FDALabel).
- Develop AI models (SafetAI Initiative) to assess drug safety.
- Develop tools to mine and analyze CDER's Science and Research Investment Tracking Archive (SARITA) database using natural language processing approaches.

» Collaborating with CTP to create Advanced Semantic Search and Indexing of Text for Tobacco (ASSIST4Tobacco) – a novel tool that uses semantic indexing to search tobacco authorization applications.

2. Alternative Methods and Knowledge Bases

» Developing the following:
- Advanced DILI prediction models for FDA-regulated products like drugs and supplements.
- Opioid Agonists/Antagonists Knowledgebase (OAK) for better management of opioid-use disorder (***page 15***).
- Molecules with Androgenic Activity Resource open-access platform for assessing the safety profile for chemicals in various food, supplement, or cosmetic products that may affect the endocrine system and cause hormonal dysfunction.

3. Precision Medicine and Therapeutics

» Completing the final studies under SEQC2, an NCTR-led consortium effort to assess technical performance and application of emerging technologies for safety evaluation and clinical application.

4. Artificial Intelligence and Machine Learning

» Applying the most advanced AI methods using the AI4Tox program to develop new tools to support FDA regulatory science and strengthen the safety review of FDA-regulated products.

» Conducting research to harness AI in mining FDA documents for relevant information to enhance regulatory operations and applications.

» Accessing the safety profile of prospective drugs in IND applications to assist FDA reviewers.

5. Real-World Data and Real-World Evidence

» Investigating racial disparities in patients with heart failure admitted to critical care and its subsequent impact on their health.

» Analyzing safety profiles of various prescription nonsteroidal anti-inflammatory drugs (NSAIDs) to understand the sex-related differences across the U.S. population.

For more information on NCTR Bioinformatic Tools, visit: www.fda.gov/NCTRBioinformatics.

Division of Genetic and Molecular Toxicology (DGMT)

Division Leadership

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

Division Goals

» Responding to Agency needs for expertise and chemical-specific data.

» Maintaining DGMT's tradition of leadership in regulatory assay development and validation.

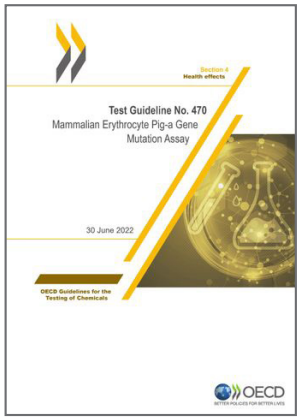
» Developing better methods for carcinogenicity testing and translation of rodent studies to human risk.

» Developing advanced in vitro toxicological models that incorporate genotoxicity endpoints.

2022 Select DGMT Accomplishments

Guidelines for Conducting Rodent Erythrocyte Pig-a *Assay*

DGMT scientists led a multinational consortium in developing a new Test Guideline (TG) for conducting the rodent erythrocyte *Pig-a* gene mutation assay. The assay is used by the FDA to evaluate the carcinogenic hazards of regulated substances. DGMT provided recommendations in 2021, which cleared the way for the TG to be published in June 2022 by the Organization for Economic Co-operation and Development. This guideline will ensure that data submitted for regulatory safety assessments of most FDA-regulated products are of uniformly high quality.



Mutation Analysis Using Error-Corrected Next Generation Sequencing

Error-corrected Next Generation Sequencing (ec-NGS) is a potentially powerful approach for evaluating rare mutations directly by the changes they make in the DNA sequence of the genome. Mutation is used by the FDA in safety evaluations of regulated products as a biomarker of carcinogenicity. DGMT scientists successfully conducted ec-NGS analyses in bacteria, *C. elegans*, and mammalian cells, including the cells from an organotypic tissue model, using two platforms—Duplex Sequencing and PacBio HiFi Sequencing. PacBio HiFi sequencing was also used to evaluate the mutagenicity of Molnupiravir, a drug given Emergency Use Authorization for treating COVID-19 patients (*Environmental and Molecular Mutagenesis*).

In 2022, DGMT scientists:

- Collaborated with other FDA Centers/Offices on 17 projects
- Gave seven presentations at NCTR Science Day
- Participated in 16 FDA working groups and committees/subcommittees and 37 external working groups
- Presented at NIH/FDA COVID-19 Research Workshop and the UAMS Systems Pharmacology and Toxicology Workshop at NCTR
- Received eight competitive intramural-funding awards (CDER Ofice of New Drugs, CDER Office of Pharmaceutical Quality, CTP, NTP, and FDA Office of Women's Health)
- Received six internal awards including an FDA Group Award, and five NCTR awards that included Excellence in Laboratory Science, NCTR Director's Award, and three Special Acts Awards
- Submitted 20 articles for peer-reviewed journals

DGMT Colloborations

» DGMT researchers collaborated with CDER to use CarcSeq—an ec-NGS technique that quantifies expansions of Cancer Driver gene Mutations (CDMs)—to detect the non-genotoxic carcinogen, lorcaserin (Belviq), in treated rats.

» DGMT scientists led or participated in the Health and Environmnetal Sciences Institute (HESI)/ Genetic Toxicology Technical Committee (GTTC) that explored the advancement of genetic toxicology using ec-NGS. DGMT collaborated with members of the committee such as the University of Ottawa, Health Canada, and TwinStrand Biosciences in a multi-lab study on analyzing mutations, including CDMs by CarcSeq, in mice exposed to an environmental mutagenic carcinogen (*Nature*).

» DGMT collaborated with the CDER *N*-Nitrosamine Drug Impurity Task Force to optimize the Ames test for detecting the mutagenicity of nitrosamine drug impurities and *N*-Nitrosamine drug substance-related impurities and to develop follow-up in vitro mammalian-cell assays to further evaluate Ames findings. This study was funded by CDER and DGMT researchers led monthly presentations to the Task Force on project progress and presented at the American College of Toxicology and Association for Affordable Medicines annual meetings on preliminary findings (*Archives of Toxicology* and *ALTEX*). DGMT also collaborated with members of the HESI/GTTC to optimize the Ames test for detecting the mutagenicity of nitrosamines by testing several nitrosamines as part of a multi-lab project with contract research organizations and industry participants (CDER supported).

Ongoing Research Projects

» Evaluate high-content high-throughput genetic toxicology using metabolically active hepatic-cell lines and primary-hepatic cells from humans

» Analyze genetic toxicology using a panel of 14 human-cell lines, each expressing a different human drug-metabolizing enzyme

» Evaluate mutagenicity of drug impurities in support of the CDER Nitrosamine Drug Impurity Task Force

» Validate study of vitrocell exposure systems to investigate the in vitro toxicity of electronic nicotine delivery systems at the air-liquid interface of human airway-tissue models

» Develop an in vitro system to evaluate the disease-related toxic effects of inhaled aerosols and vapors in human airway-tissue models

» Develop an in vitro co-culture system to test the adverse effects of drugs and their metabolites on human embryo-fetal development

» Develop a microphysiological system for evaluating Zika virus sexual transmission using a testicular model

» Develop a microphysiological system for evaluating antibody therapies targeting viral infections during pregnancy: a Zika virus case study

Division of Microbiology (DM)

Division Leadership

- Division Director – Steven Foley, Ph.D.

2022 Select DM Accomplishments

Food Safety and Virology: Antimicrobial Resistance and Virulence

» Evaluated the role of bacterial plasmids in antimicrobial resistance dissemination between bacterial pathogens, which could lead to more difficult-to-treat infections (*Frontiers in Microbiology*, *Microorganisms*, *Microbiology Resource Announcements*).

» Characterized companion animal-associated alphacoronaviruses that were detected in human patients with acute respiratory illness from different countries (*Emerging Microbes & Infections*).

» Characterized virulence factors that can potentially contribute to increased ability of *Salmonella enterica* to cause foodborne infections (*Frontiers in Artificial Intelligence* and *Foodborne Pathogens and Disease*).

Microbiome and Biological Interactions

» Continued studies on the of exposure of xenobiotic compounds, including arsenic, bisphenol AF, and triclosan on the microbiome and host responses through NTP-funded efforts. These efforts are informing risk assessments of the test compounds (*International Journal of Molecular Sciences*).

» Coordinated with NCTR's Office of Scientific Coordination to sequence studies on multiple bacterial species that are underrepresented in microbial sequence databases. These sequences were made available in public databases and described in multiple *Microbiology Resource Announcement* publications (February 2022, April 2022, October 2022, November 2022, November 2022).

» Used transcriptomic analyses to assess the impact of continuous exposure to antibiotic-impregnated catheters on biofilm formation by the human pathogen *Pseudomonas aeruginosa*. The formation of biofilms can lead to difficulty in eradicating bacterial populations (*Data*).

In 2022, DM scientists contributed to or participated in the following outreach events:

- **ARA Project Scope** – Dr. Steven Foley was featured at the ARA Project Scope webinar and was also featured in a Research Matters (PDF) article in *Arkansas Money and Politics*.
- **FDA Grand Rounds** – Dr. Peter (Seongjae) Kim presented key efforts related to microbial contaminants of tattoo and permanent makeup inks.
- **NCTR Science Day** – DM scientists gave nine presentations.
- **European Food Safety Authority One Health Conference (EFSA)** – presented microbiome-related research.
- **2022 FDA Foods Program Regulatory Science Conference** – DM scientists gave six presentations.
- Seminar series featuring speakers from academia and other FDA entities every other month. Each session averaged 20-30 participants.

Microbial Contaminants Detection

» Developed and evaluated approaches to detect and enumerate *Burkholderia cepacia complex* (BCC) in pharmaceutical products. These improved and widely accessible detection methods for BCC are important to limit patient exposure to BCC pathogens linked to multiple disease outbreaks (*Microorganisms* – April 2022 and June 2022).

» Collaborated with CFSAN to conduct survey studies to assess microbial contamination levels of tattoo and permanent makeup inks available on the U.S. market. The studies determined that contamination of the ink products is a potential concern, as multiple inks were found to contain microorganisms (*Microorganisms*).

» Used sequencing methods to characterize diverse groups of *Staphylococcus aureus* pathogens associated with human infections (*Microbiology Resource Announcements* and *Canadian Journal of Microbiology*).

» Optimized and standardized methods for the production and purification of spore samples to be used in the sporicidal efficacy assessment of compounded drug products (*Journal of Industrial Microbiology and Biotechnology*).

Ongoing Research Projects

» Evaluating a recombinant coronavirus spike protein to generate reagents, study cell interactions, and and enhance antibody-dependence

» Discovering intracellular and extracellular signaling pathways and mechanisms contributing to complement activation and coagulopathies associated with coronavirus infections

» Assessing the role that the microbiome may play in the toxicity of xenobiotics

» Validating isolation and identification of nontuberculous mycobacteria associated with tattoo-related skin infections in a multi-lab setting

» Detecting microbial contaminants, including anaerobic bacteria, in tattoo inks and other related products

» Establishing standardized methods for sporicidal efficacy assessment and building up an efficacy database of sporicidal products to support FDA's regulation on drug compounding

» Evaluating antimicrobial, antibiofilm, and cytotoxicity activity of nanoparticles (Se, V) and nanostructured surfaces (Ti, Cu) and transcriptomic and proteomic response of multidrug resistant bacteria

» Evaluating tools to efficiently assess antimicrobial resistance and pathogenicity-related functions of plasmids in bacterial pathogens

» Evaluating in vitro vaginal-tract models to assess the biotherapeutic potential of *Lactobacillus* toward Toxic Shock Syndrome Toxin-1-producing *Staphylococcus aureus*

» Analyzing non-sterile pharmaceutical products using metagenomics to detect microorganisms

Division of Neurotoxicology (DNT)

Division Leadership

- Division Director – John Talpos, Ph.D.

The Division of Neurotoxicology performs research on diverse topics to meet the current and future needs of the agency. Human neurotoxic insults are modeled in animals to generate the data necessary to advise regulation. This work is complemented by research with alternative models, such as cell culture and non-mammal organisms, to understand mechanisms of toxicity, and to describe drug/drug and drug/gene interactions. Recent division highlights include completion of two large animal studies designed to address data gaps in our knowledge of regulated products, new in vitro studies examining off-label use of products, and work with non-invasive biomarkers of neurotoxicity that could have rapid translational value.

2022 Select DNT Accomplishments

The Acute Neurotoxic Effects of Ketamine During Adolescence

Clinical trials show ketamine can quickly alleviate the acute symptoms of depression. The research community wants to test the effects of ketamine for treatment of different indications and in an adolescent population. However, comprehensive safety data for ketamine in children does not exist. In collaboration with CDER, division scientists tested ketamine in adolescent and adult rats. The data showed that adolescent rats do not have an increased sensitivity to the neurotoxic effects of ketamine. These data will impact future guidelines on the acceptable doses of ketamine in future clinical trials.

Cannabidiol Exposure and Its Effects

In collaboration with FDA's OCS, CFSAN, and CDER, division researchers completed a multiple-year assessment of CBD effects early in life on brain development and cognitive performance in the rat. Additionally, researchers studied the possibility of early-life exposure to CBD altering the immune response later in life. These studies are expected to determine if the brain's "defense mechanisms" against infection and injury change in response to these exposures. Data from these studies are being analyzed and will fill data gaps and guide future regulatory decisions.

In 2022, DNT scientists:

- Published 13 articles
- Presented eight posters at NCTR Science Day
- Gave nine presentations internal to FDA and 12 to external organizations
- Received competitive intramural-funding awards for three division protocols from PHCE and OCS
- Collaborated with other FDA centers on 25 ongoing protocols
- Organized a session and presented at multiple sessions on "Biomarkers of Neurotoxicity" at the XVIth International Congress of Toxicology
- Contributed to groups such as HESI, Zebrafish and Frog Interest Group, the Critical Path Instititute, and others

Using Zebrafish Model to Explore Arsenic-Related Neurotoxicity

The rat is a powerful and predictive research model, but is slow compared to alternative research models. In collaboration with the NCTR-led Perinatal Health Center of Excellence (***page 15***), DNT researchers used zebrafish to explore how arsenic causes neurotoxicity. Results from this work were presented at various meetings in 2022 and were published in *Neuroscience Letters*. Expanding on the results, DNT plans to use zebrafish to study arsenic and cadmium exposure in combination. Ultimately, zebrafish may allow researchers to study toxicity faster and at a lower cost. This is particularly useful when studying the toxicity of co-exposure, as frequently occurs with heavy metals.

Ongoing Research Projects

Blood-Brain Barrier-Related Neurotoxicity

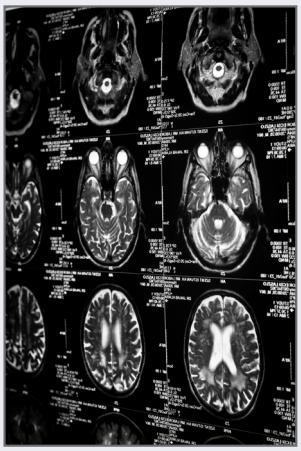
The brain is a sensitive organ and exists in a micro-environment maintained by the blood-brain barrier (BBB). Failure of the BBB will compromise this micro-environment and can lead to brain damage. DNT scientists are currently investigating changes to BBB-related proteins in a rat model of Alzheimer's disease (AD) and are investigating the interaction between hyperglycemia and AD on brain vasculature. To complement these animal studies, "brain-on-a-chip" technology is being used to better understand the mechanisms behind BBB dysfunction with the goal of better modeling AD.

Opioid and CBD Interaction with an In Vitro Model of Human Brain Developmen

CBD use is purported to reduce the symptoms of opioid withdrawal. Despite the lack of FDA approval for this condition, some individuals with opioid-use disorder are turning to unregulated CBD to manage symptoms during pregnancy. Consequently, these children are exposed to CBD and opioids before birth. DNT scientists were awarded a PHCE grant to study the interaction between opioids and CBD with an in vitro model of human brain development. This approach allows us to model the interaction between opioids and CBD (and its metabolites) on human brain development more efficiently than using animal data alone. These studies will shed light on the risks associated with certain drugs used outside of their clinical setting.

T_2 Magnetic Resonance Imaging (MRI) as a Biomarker of Neurotoxicity

Unlike the heart or lungs, the brain cannot be directly observed at work. Most tools to study neurotoxicity require destruction of the brain. Neurotoxicity can only be assessed once in each study animal. Advanced imaging methods like MRI are an exception to this. When using MRI, tissue is exposed to a strong magnetic field. This causes the protons in water molecules to align to this magnetic field and oscillate at a specific resonant frequency. When a brief external pulse of electromagnetic radiation is applied, these protons absorb the energy and then radiate it, producing a brief signal. This signal is used to construct a picture of the brain. DNT scientists are studying if this picture can act as a biomarker of neurotoxicity. If so, neurotoxicity can be assessed multiple times in one animal. Ultimately this means more comprehensive toxicity assessments can be performed using fewer animals. Such an approach could improve the safety of future drugs while reducing the number of animals used in biomedical research.

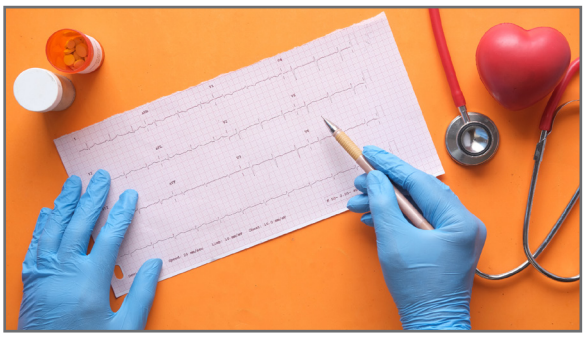


For more information on Neurotoxicology, click here.

Division of Systems Biology (DSB)

Division Leadership

- Division Director – Laura Schnackenberg, Ph.D.
- Deputy Director – Jessica Hawes, Ph.D.
- OMIC Branch Chief – Richard Beger, Ph.D.



2022 Select DSB Accomplishments

Clinical/Translational Omics Biomarkers

» Qualified protein biomarkers for prediction of anthracycline-associated cardiotoxicity through evaluation of plasma from 85 breast cancer patients treated with doxorubicin and cyclophosphamide (manuscript under preparation).

» Used an untargeted mass spectrometry-based metabolomics method to evaluate changes in metabolic activity in accordance with changes to the gut microbiome induced by treatment of mice with cefoperazone (*Metabolites*).

» Reported microRNA-34a-5p as an early circulating preclinical biomarker of doxorubicin-induced chronic cardiotoxicity (*Journal of Applied Toxicology*).

Predictive Toxicology

» Developed a spectroscopic data-activity relationship (SDAR) model that was validated by collaborators at the National Center for Advancing Translational Sciences and can be used to identify drugs that can cause clinical cardiotoxicity due to human ether-a-go-go related gene (hERG) inhibition. In addition, a structural characteristic referred to as a toxicophore was identified for drugs that have the potential to block the hERG channel. The identified toxicophore is composed of two aromatic rings and an amino group, wherein special attention should be paid to new drugs containing this feature, as they may have greater potential to induce cardiotoxicity.

In 2022, DSB scientists contributed to or participated in the following outreach events:

- **FDA's 2022 Multi-Component Biomarker Workshop** – co-organized the workshop and contributed to the associated white paper that will be published in early 2023.
- **FDA 10th Annual Scientific Computing Days** – two DSB breakout sessions and one poster presentation (PDF) (***page 11***).
- Hosted internal guest lecture by FDA Principal Deputy Commissioner Dr. Janet Woodcock – *"Integration of Research and Regulation: an Ongoing Challenge."*
- **Metabolomics 22 International Conference** – presented *"QC Best Practices in Metabolomics Workshop."*
- **Metabolomics Association of North America Conference** – presented *"A Community-Led Initiative to Strengthen Quality Assurance and Quality Control Practices and Reporting in Untargeted Metabolomics Research."*
- **NCTR Science Day** – seven DSB posters were presented.

» Worked to help establish reliable and reproducible toxicity and/or functional assays for different liver cell types maintained in a microphysiological system (MPS). Once established, the liver MPS can be used to evaluate the potential of therapeutics to cause liver injury (*Current Protocols*).

» Investigated the use of human-induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) for cardiac safety assessment in nonclinical studies to gain a better understanding of the variability of the human-based in vitro system to predict drug-induced cardiotoxicity (*Toxicological Sciences*).

Therapeutic Safety and Product Center Support

» Assessed binding potential of montelukast to a panel of proteins containing targets/receptors related to drug safety, G-protein-coupled receptors, ion channels, and transporters expressed in the brain.

» Evaluated the roles of opioids in neural-tube defect formation, and drug-related maternal toxicity, specifically hypoxia, at gestational day eight in mice. Additionally, evaluated lipid changes in areas of exencephaly in the fetuses of exposed dams.

» Established a mouse tumor model to assess acute inflammatory toxicities including cytokine release syndrome, neuroinflammation, and neurotoxicity following chimeric antigen receptor (CAR) T-cell therapy.

In 2022, DSB scientists:

- **Published 20 articles**
- **Gave 24 oral presentations — 8 FDA internal and 16 external**
- **Presented 29 posters — 10 FDA internal and 19 external**
- **Provided research support services to other NCTR divisions and FDA centers/ offices via seven support projects**
- **Conducted 48 DSB research projects that included collaborators from other FDA centers/offices**
- **Received 22 funding awards for DSB studies — 11 competitive intramural-funding awards, seven CDER project-funding awards, and four COVID supplemental-funding awards**
- **Received 17 accomplishment awards**
- **Participated in approximately 18 FDA working groups and committees/ subcommittees and 20 external working groups**

Response to Health Threats/Emergencies

» Effects of SARS-CoV-2 infection and anti-viral therapy during development:

- Completed ID50 (infective dose needed to produce infection in 50% of animals), time-course, and other studies in non-pregnant mice at the Regional Biocontainment Laboratory at UTHSC, which provided necessary preliminary assessment and characterization data of the humanized mouse model that will be used in larger studies to evaluate the effects of SARS-CoV-2 infection and anti-viral therapy during pregnancy, and provided information to select the SARS-CoV-2 variant-of-concern viral dose.
- Established an hACE2-KI mouse breeding colony that is being used to provide the time-mated animals needed to accomplish the overall aims of the protocol and the study in pregnant animals.
- Completed a pilot study with infection in timed pregnancies with harvested tissues at different gestation days for histopathological assessment.

» Employed imaging mass spectrometry to define the *N*-glycan profiles of co-localized SARS-CoV-2 and immune-cell infiltrates in tissues from humans and mice infected with COVID-19.

Office of Regulatory Compliance and Risk Management (RCRM)

Office Leadership

- Associate Director – Rajesh Nayak, Ph.D.

Regulatory Compliance and Risk Management (RCRM) reports directly to the NCTR Center Director and is responsible for the overall safety and security of Jefferson Laboratories (JL) employees. RCRM's mission is to 1) ensure the safety and security of the JL employees; 2) ensure research conducted at NCTR is compliant with state and federal regulations; and 3) assist in the assurance of quality and integrity of the research data.

Regulatory Compliance

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

» ensure regulatory compliance in chemical, biological, radiological, and environmental safety;

» maintain inventories of hazardous chemical and biological materials;

» oversee safety of employees under the medical and animal surveillance programs; and

» provide necessary job-related safety training to employees.

In addition, RCRM also maintains the following compliance programs:

» Nuclear Regulatory Commission License

» Arkansas Department of Environmental Quality Air and Water safety programs

» Drug Enforcement Agency controlled substances

» Occupational Health Unit (OHU) Medical Surveillance Programs

» Environmental Protection Agency hazardous waste disposal

» AAALAC program accreditation

» 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.

RCRM received a report from the Hazardous Reporting System indicating that the newly constructed steps leading to/from the cafeteria could be a trip hazard. RCRM coordinated with FDA's Office of Facilities Engineering and Mission Support Services and facility maintenance contractor (DCT, Inc.), to paint the edges of the cafeteria steps bright yellow to allow greater visibility when using those stairs.

Customer Services

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:

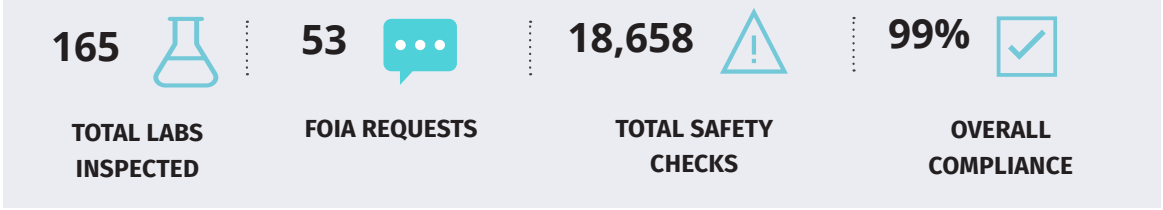
» provide safety updates through the JL Environmental, Safety, and Health Committee meetings;

» respond to emails/phone calls/anonymous safety reporting;

» advise staff on personal protective equipment; and

» 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.

Safety, Security, Health, and Records



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.

Partnerships

RCRM staff support the mission of the FDA Office of Laboratory Safety (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 (ESOH) program organized under the Office of Facilities Engineering and Mission Support Services (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 lab/ vivarium during the COVID-19 pandemic, and FDA's Contact Tracing and Return-to-Facilities programs.

2022 RCRM Activities and Accomplishments

- Trained 43 staff members on New Employee Safety Orientation from April-Dec 2022
- Successfully completed an NRC audit
- Trained 177 staff members on NCTR-specific laboratory safety
- Inspected 165 labs with a 99% overall compliance rate for lab safety. Mandatory annual report submitted to OLS
- Initiated a new contract for certifications of biosafety cabinets – 92 biosafety cabinets, three change stations, and two laminar flow units certified
- Conducted campus fire drills
- Trained 20 NCTR staff on NCTR-specific radiation safety training

RCRM staff serve on multiple FDA and JL safety and security committees/working groups:

- FDA COVID-19 contact tracing program
- FDA Cyber & Data Security Advisory committee
- FDA Exposure Information Communication & Reporting (EICRU)
- FDA Good Clinical and Nonclinical Practices Council
- FDA Human Subject Protection/Bioresearch Monitoring
- FDA Institutional Scientific Collections
- FDA Mentoring program
- FDA Office of Laboratory Safety (OLS) council and associated sub-committees
- FDA OLS Biological Safety and Toxins Safety
- FDA OLS Chemical Safety
- FDA OLS Dual Use of Concern
- FDA OLS Environmental Safety and Health Council
- FDA OLS Good Laboratory Practices
- FDA OLS Institutional Biosafety Council & Committee (Weekly Administrative Meetings)
- FDA OLS LQMS Working Group
- FDA OLS Radiological Safety
- FDA One Health Initiatives
- FDA OSEM COOP
- FDA Quality Resource and Guidance
- FDA Records Liaison and Reports clearances
- FDA Regulatory Policy Council
- FDA Security Operations and Emergency Management Continuity of Operations
- FDA Traineeship program
- JL Animal Welfare (IACUC, AAALAC, OLAW etc.)
- JL Environmental Safety and Health
- JL Radiation Safety

Office of Management (OM)

Office Leadership

- Associate Director for Operations & Office of Management – Denny Skiles
- Planning and Resources Management – Barry W. Downing & Richard "Rick" Keach
- Executive Programs and Services – Moses "Robby" Robinson
- Communications Branch – Tonya Vyas

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 ~5K requisitions in FY22 to support NCTR research and NCTR's annual Advanced Acquisitions Plan and Acquisitions Strategy. 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 approved all Center travel, oversaw government credit cards, administered payroll funds, and managed requisitions to ensure that appropriated funds were spent within 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 FY22. PRM also managed reimbursable IAAs, shared allowances, Cooperative Research and Development Agreements, and other transfers from external.

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.

Budget and Resource Planning

Executive Programs and Services

The Executive Programs and Services (EPS) staff provide human capital management; administer NCTR's Research Training Program, Awards and Recognition Program, and Property Management; and implement the Agency's Performance Management Program. EPS provides additional administrative and logistical support services to include mail service, conference room management, and quality of work-life programs.

Diversity, Equity, and Inclusion (DEI)

In 2022, NCTR's DEI Committee sponsored several diversity events and commemorative programs designed to promote and champion diversity, equity, and inclusion in the workplace including:

- Highlighted NCTR's diverse workforce and promoted a more inclusive culture through the "Faces of NCTR" campaign, highlighting employees from various ethnic backgrounds during diversity awareness months.
- Sponsored a virtual Pride Month trivia game to increase employee awareness and knowledge about the LGBTQ+ movement.
- Sponsored—with Blacks in Government (BIG)—NCTR's Virtual Diversity Food Fair, showcasing cuisine from around the world.
- Increased outreach to the veteran community and under-represented minority groups at virtual job fairs and employer panels at minority-serving institutions and the Little Rock Air Force Base.

NCTR enhanced outreach efforts to increase representation of underrepresented groups through the use of professional social media platforms and diversity job boards to advertise vacant positions and research fellowship opportunities. NCTR presented at virtual career fairs targeting minority STEM candidates.

Federal Employee Viewpoint Survey (FEVS) Workgroup

NCTR's FEVS workgroup launched a seminar series on topics designed to increase employee engagement and inclusivity and create a healthier work environment. Topics included "Creating a Values-driven, Informed, and Passionate Workplace" and "Generational Diversity in the Workplace." Over 60 employees across Jefferson Laboratories participated in both seminars. Based on positive feedback, the FEVS workgroup developed topics for future seminars. Additionally, NCTR facilitated team-building sessions, upward feedback surveys for supervisors, and small focus-group discussions. The FEVS workgroup helped sponsor "Night at the Ballpark"—open to all Jefferson Labs employees and their families to see a local minor league baseball game. This event 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 Jefferson Labs.

NCTR Personnel

(Numbers as of 3/29/2023)

Research Scientists	66
Staff Fellows/Visiting	81
Support Scientists	55
Administrative	81
Contractors	187
ORISE	38
Student Interns	6
Total Staff	**514**

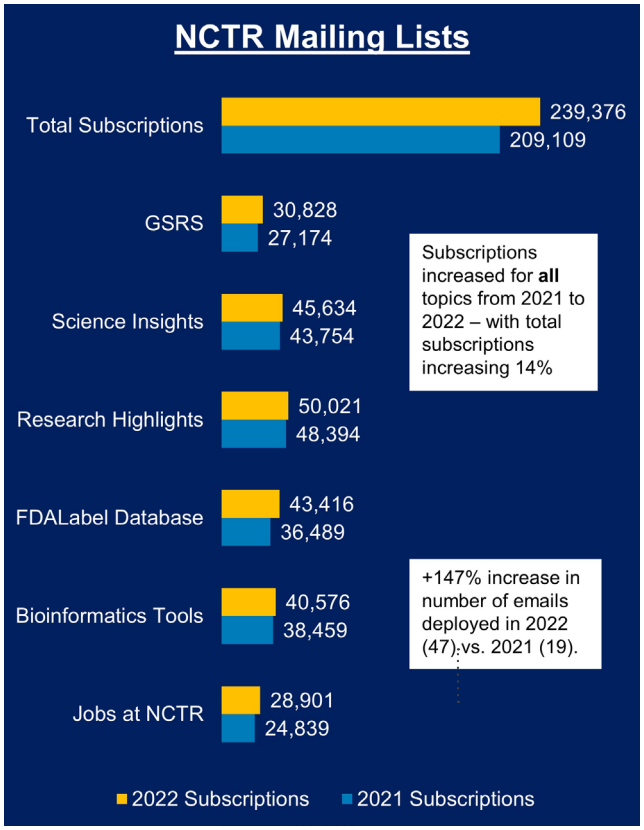
Office of Management Staff at "Jefferson Labs Night at the Ballpark."

Communications Branch

The NCTR Communications Branch (Comms) manages and develops NCTR's communications efforts such as email-subscriber list management and messaging, virtual-conference support, graphics support services, media inquiries, press releases, reports, Section-508 compliance, and web content management. In 2022, this included the review and cleanup of 500+ media items and 250+ web pages. Comms represents NCTR on 8 FDA-level councils/working groups.

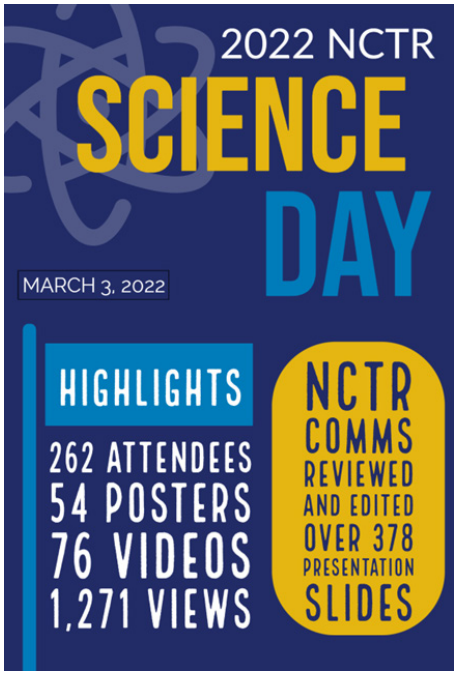
Writing, Editing, and Creative Support

- 750+ slides reviewed to ensure editorial quality of PowerPoint presentations
- 248 informative campus-wide emails
- 115+ researcher bio-sketches online
- 76 videos with 1,271 views
- 37 employee profiles (diversity, equity, & inclusion)
- 13 Research Highlights
- 13 media inquiries
- 10 external brochures & 10 event flyers
- 3-page print ad for *Nature* special issue



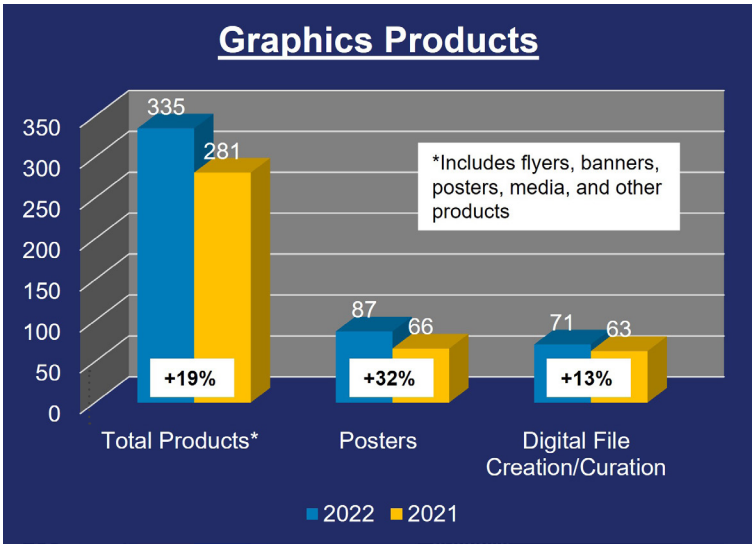
NCTR-, FDA-, and Public-Event Support

Comms supports in-person, virtual, and hybrid events through email promotions, content review, web promotion, press releases, remote-meeting coordination, event recordings, conference booth design and support, and more.



NCTR 360 Internal Newsletter

The NCTR 360 is a comprehensive information outlet. In the last quarter of CY22, Comms redesigned the NCTR 360 from a quarterly PDF to a dynamic web-based design that allows for real-time updates and measurement of readership. Comms wrote and published 92 newsletter articles in 2022, with the 46 articles published on the new platform from Oct-Dec 2022 receiving 2,570 total views.



If you are interested in subscribing to NCTR mailing lists please visit our website and subscribe with your email address.

Jefferson Labs
CAMPUS IMPROVEMENTS

Exterior Lighting Project

In 2022, new exterior lighting was added to the parking lot and main entrance into the campus, as well as along walkways. Prior to this project, low visibility made it difficult for personnel to safely walk around campus after hours or during bad weather.

Distributed Antenna System Update

Jefferson Labs campus implemented a Distributed Antenna System (DAS) to provide reliable cellular service throughout the Jefferson Labs campus buildings and centrally located outside areas.

In 2022, the DAS contractors completed the on-campus installation of equipment required to distribute the cellular signal that is brought in (via fiber) by the three carriers: Verizon, AT&T, and T-Mobile.

U.S. FOOD & DRUG ADMINISTRATION

National Center for Toxicological Research

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Jefferson, AR 72079-9501

To learn more about NCTR, visit

NCTRResearch@fda.hhs.gov

www.fda.gov/nctr

www.fda.gov/nctrannualreport